



FYI-0702-01431

MR 60797

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

Document Control Office

July 22, 2002

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Dear Document Control Office:

In compliance with the National Toxicology Program's (NTP) mission to keep our colleagues informed of the current NTP findings during ongoing studies, a copy of the Pathology Working Group (PWG) report and the Summary Pathology Tables for the chronic Dose Feed study on TRANSGENIC MODEL EVALUATION II (ASPARTAME) (22839-47-0) are enclosed for your review.

The NTP assembles a Pathology Working Group to review every study and to resolve any differences between the study laboratory and quality assessment pathology evaluations. Please note that the PWG conclusion of the study results is based solely on the pathology for this study and may not reflect final NTP conclusions. In determining final conclusions, the NTP assesses a broad array of information that includes other results from this study and historical control data.

The Summary Pathology Tables contain the Incidence Rates of Neoplastic and Non-neoplastic Lesion data and the Statistical Analysis of Primary Tumors data pertaining to the laboratory animals. All study data are subject to an NTP retrospective audit and the interpretation may be modified based on the findings.

A wide variety of NTP information is also available in electronic format on the world-wide web, for example, the NTP Annual Plan, abstracts of NTP Reports, study data, and the status of all NTP studies. To view this information requires access to the internet and a Web browser such as Netscape Navigator or Internet Explorer. To access the NTP home page, use the URL <http://ntp-server.niehs.nih.gov/>. Comments on the usefulness of this site and suggestions for improvement are encouraged.

Please contact Central Data Management (CDM) at (919)541-3419 if you have any questions. You may also fax your requests for information to CDM at (919)541-3687 or send them via e-mail cdm@niehs.nih.gov.

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Hard copies of documents such as NTP Technical Reports, short-term Toxicity Reports, and the Report on Carcinogens are available from the Environmental Health Information Service (EHIS). You can contact EHIS by phone at (919) 541-3841, by fax at (919)541-0273, or by e-mail at ehis@niehs.nih.gov.

Sincerely,



Sharon M. Soward
Project Officer, CDM
Environmental Toxicology Program

Encls: PWG Report and Pathology Summary Tables for Tg.AC, P53 +/-,
and P16 +/- Mice

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PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT

2002 JUL 30

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TRANSGENIC MODEL EVALUATION OF THE THIRTY-NINE WEEK
PRECHRONIC TOXICITY/CARCINOGENICITY STUDY OF ASPARTAME (ASP)
FOLLOWING DOSE FEED ADMINISTRATION IN MALE AND FEMALE NTP²
HEMIZYGOUS Tg.AC (C99033/9033-01), HETEROZYGOUS P53+/- (C99033/99033-02)
AND HETEROZYGOUS P16+/- (C99033B/99033-03) MICE

Prepared by:

Philip H. Long, DVM, PhD, DACVP
Pathology Working Group Chairperson

Pathology Associates-A Charles River Company
6217 Centre Park Drive
West Chester, OH 45069

2002 AUG 12 AM 10:19

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Submitted to:

National Toxicology Program/NIEHS
Research Triangle Park, NC

April 15, 2002

The pathologist performing this review, Dr. Philip H. Long, has had no involvement with any laboratory or organization concerned with this study other than NIEHS, and has not been involved in the origination or any previous review of data from this study.

PATHOLOGY WORKING GROUP CHAIRPERSON'S REPORT

Transgenic Model Evaluation Of The Thirty-Nine Week Prechronic Toxicity/Carcinogenicity Study Of Aspartame (ASP) Following Dose Feed Administration In Male And Female NTP Hemizygous Tg.AC (C99033/9033-01), Heterozygous P53+/- (C99033/99033-02) And Heterozygous P16+/- (C99033B/99033-03) Mice

PWG Participants: Drs. P. H. Long (PAI - PWG Chairperson), R. Herbert (NIEHS), A. Nyska (NIEHS), G. Flake (NIEHS), P. Little (PAI – Neuropathology expert), D. Dixon (NIEHS), C. Shackelford (EPL - QA Pathologist), G. Hill (observer), W. Lieuallen (observer).

Date: March 12, 2002

Site: NIEHS, Research Triangle Park, NC

INTRODUCTION

The Pathology Working Group (PWG) was convened to evaluate selected slides from three strains of transgenic mice that were given Aspartame (ASP) administered by dosed feed for 39 weeks.

Prior to convening the PWG, the original Post Experiment Information System Individual Animal Necropsy Records, the Toxicology Report, selected TDMS PEIRPT reports, and selected hematoxylin and eosin stained microscopic slides from the 39-week ASP study were submitted to Pathology Associates International (PAI) for Pathology Working Group Chairperson review. The slides submitted were originally examined and the data reported by BioReliance. This was followed by an EPL Quality Assessment Pathologist (QAP) review of the data and slides. The study and quality assessment pathologists for the study were Dr. L. L. Lanning from BioReliance and C. C. Shackelford from Experimental Pathology Laboratories, Inc. (EPL®), respectively.

The PWG Chairperson examined all slides from nine randomly selected high dose (50,000 ppm) male and female¹ mice of each strain sacrificed at the termination of the study and nine randomly selected control mice of each strain (both sexes). These animals are indicated by C.R. (Complete Review) beneath the histology number on the work sheets. Also, all tumor diagnoses from all animals in all groups were reviewed. In addition, all lung sections from all groups of male Tg.AC mice were reviewed for the presence of proliferative lesions. The PWG Chairperson also examined all brain sections from all Tg.AC mice. Findings were tabulated using Slide Review Work Sheets (SRWS) as presented in the Pathology Quality Assessment report.

¹For the Tg.AC strain, all slides were reviewed from eight randomly selected high dose female mice sacrificed at termination of the study.

The experimental design for this study is presented below:

ASP 39-WEEK PRECHRONIC STUDY						
Dosage (ppm)	Tg.AC Hemizygous		p53+/- Heterozygous		p16+/- Heterozygous	
	Males	Females	Males	Females	Males	Females
0	15	15	15	15	15	15
3,125	15	15	15	15	15	15
6,250	15	15	15	15	15	15
12,500	15	15	15	15	15	15
25,000	15	15	15	15	15	15
50,000	15	15	15	15	15	15

SUMMARY OF PWG FINDINGS

This review confirmed that, under the conditions of this study, ASP was not carcinogenic when administered by dosed feed to hemizygous Tg.AC, heterozygous p53+/-, or heterozygous p16+/- mice. As expected in this type of review, some terms and diagnoses were changed; however, overall agreement between the study pathologist, QA pathologist, and PWG Chairperson was very good. The pathology review confirmed, did not confirm, or reported the following observations:

Tg.AC Mice

- Confirmed an absence of brain neoplasms.
- Confirmed a slightly higher incidence of alveolar bronchiolar adenomas in ASP-treated males.
- Did not confirm the presence of cytoplasmic vacuolization in the brain of treated males or females.
- Did not confirm a decrease in the incidence or severity of splenic hematopoietic cell proliferation in high dose males or females.
- Did not confirm a decrease in the incidence of adrenal zona reticularis cytoplasmic vacuolization in high dose females.

p53+/- Mice

- Confirmed an absence of ASP-related morphologic tissue effects, including an absence of brain neoplasms.
- Did not confirm an increase in the incidence of splenic lymphoid hyperplasia in high dose females as reported by the quality assessment pathologist.

p16+/- Mice

- Confirmed an absence of brain neoplasms.
- Did not confirm increased incidences of cytoplasmic vacuolization of periportal hepatocytes in high-dose males or females.
- Did not confirm a number of tumors diagnosed by the study pathologist as hemangiosarcomas or malignant ovarian thecomas (these were found to represent histiocytic sarcomas).

CONDUCT OF THE PWG

Prior to the PWG, the chairperson reviewed the laboratory reports and the original study pathologist's pathology narratives, the summary and individual animal pathology tables, the quality assessment reports, and selected microslides from the studies. In consultation with Dr. J. F. Mahler (NIEHS), the PWG chairperson then selected a set of slides for review by the PWG. This included representative examples of any treatment-related lesions, unusual lesions, and lesions for which there were differences of opinion in diagnosis among the SP, QAP, and/or PWG Chair. The PWG consensus opinion for each slide examined, including any additional diagnoses made by the PWG, was recorded on the PWG Chairperson's worksheets attached to this report. The pathology findings were then recorded on the PWG modules.

BACKGROUND INFORMATION

Tg.AC Mice

According to the study report, there were no ASP-related effects on survival, clinical signs, group mean body weights, food consumption, or gross lesions. In males, a significant increase in mean absolute brain weight was noted in the 50,000 ppm dose group and a significant increase in mean brain weight ratios were noted in the 25,000 and 50,000 ppm dose groups.

Microscopically, no brain neoplasms were detected in this study. There was a slightly higher incidence of alveolar bronchiolar adenomas in ASP-treated males. Cytoplasmic vacuolization was reported in the brain of 1 treated 25,000 ppm male and 3 treated females (one each from the 6,250, 12,500, and 25,000 ppm groups). A decrease in the incidence and/or severity of splenic hematopoietic cell proliferation was reported in high dose males and females. A decrease in the incidence and severity of adrenal zona reticularis cytoplasmic vacuolization was reported for high dose females. Slight increases in the incidences of unilateral sertoli cell and germ cell degeneration were noted in ASP-treated males.

p53+/- Mice

According to the study report, there were no ASP-related effects on survival, clinical signs, group mean body weights, organ weights, food consumption, gross alterations, or microscopic alterations. Microscopically, the study pathologist reported an absence of ASP-related morphologic tissue effects, including an absence of brain neoplasms. In contrast, the reviewing pathologist reported an increase in the incidence of splenic lymphoid hyperplasia in high dose females.

p16+/- Mice

According to the study report, there were no ASP-related effects on survival, clinical signs, group mean body weights, food consumption, or gross lesions. In female p16 mice, significant decreases in mean relative lung weights were noted in the 6,250 and 25,000 ppm dose groups. Trends for decreased absolute and relative group mean lung weights were noted in all ASP treated groups of p16+/- female mice when compared to the corresponding control groups. Microscopically, no brain neoplasms were detected in this study. The incidence of cytoplasmic vacuolization of periportal hepatocytes was reported to be increased in high dose males and females.

Results of the PWG Review

Tg.AC Mice

Brain

This review confirmed an absence of brain neoplasms in this study. The cytoplasmic vacuolization reported in the brain of 1 treated 25,000 ppm male and 3 treated females (one each from the 6,250, 12,500, and 25,000 ppm groups) was found to represent diffuse white matter vacuolization artifact as opposed to an actual lesion (McLarrin, 1982; Wells, 1989). Vacuoles were characterized as discrete with smoothly rounded margins with no evidence of edema, demyelination/reduced staining, cellular reaction/gliosis, or vascular reaction. The other brain alterations noted in this strain included a single 25,000 ppm female (#167) with a brain abscess, a single 6,250 ppm female (#148) with cortical neuronal necrosis that was moribund sacrificed on day 67, a 50,000 ppm male (#78) with focal cortical degeneration consistent with an infarct, and a 50,000 ppm female (#195) with non-specific focal cortical degeneration. These lesions were considered incidental and unrelated to treatment. This conclusion is supported by the observation that the FVB parent strain (FVB/N), from which these Tg.AC mice are derived, is known to be prone to spontaneous seizures and secondary neuronal necrosis (Goelz et al.) and the observation that similar lesions were not noted in the p53 or p16 strains.

Lung

There was a slightly higher incidence of alveolar bronchiolar adenomas in ASP-treated males. Histologically, these neoplasms were morphologically consistent with those previously described in rodents.

Spleen

A decrease in the incidence and/or severity of splenic hematopoietic cell proliferation (extramedullary hematopoiesis) was reported in high dose males and females. This could not be confirmed by the quality assessment pathologist, the PWG Chairperson, or Dr. J. F. Mahler (NIEHS). It was therefore agreed to use splenic hematopoietic cell proliferation incidence and severity grades as assessed by the PWG Chairperson.

Adrenal Glands

A decrease in the incidence and severity of adrenal zona reticularis cytoplasmic vacuolization was reported for high dose females. The decrease in incidence could not be confirmed by the quality assessment pathologist, the PWG Chairperson, or Dr. J. F. Mahler (NIEHS). This spontaneous, age related, gender specific degenerative lesion of the adrenal cortex was similar to the changes described in the parent strain (FVB/N) from which these Tg.AC mice are derived (J. F. Mahler, et al., 1996). In addition, both the PWG Chairperson and Dr. J. F. Mahler (NIEHS) noted that x-zone degeneration was referred to as cytoplasmic vacuolization of the zona reticularis. Though not changed, it was noted that the preferred designation for this zone is the x-zone and that the preferred diagnostic term for this alteration is degeneration (JF Mahler, et al., 1996). Dr. J. F. Mahler (NIEHS) concurred with this assessment and agreed to use adrenocortical severity grades as assessed by the PWG Chairperson. Observed differences in severity were attributed to biologic variation as opposed to a treatment effect.

Testes

Slight increases in the incidences of unilateral sertoli cell and germ cell degeneration were noted in all ASP-treated groups of male mice. In discussion with Dr. J. F. Mahler (NIEHS), it was agreed that not all testicular lesions needed to be reviewed because most were unilateral and therefore considered spontaneous and unrelated to treatment.

p53+/- Mice

Spleen

In contrast to the study pathologist, the reviewing pathologist reported an increase in the incidence of splenic lymphoid hyperplasia in high dose females. The increase in incidence could not be confirmed by the PWG Chairperson or Dr. J. F. Mahler (NIEHS). In discussion with Dr. J. F. Mahler (NIEHS), it was agreed to use splenic lymphoid hyperplasia incidence and severity grades as assessed by the study pathologist.

Miscellaneous Tumors

Tumors for which there was not agreement among the study pathologist, quality assessment pathologist, and PWG Chairperson were reviewed by the PWG. As a result, some diagnoses were changed; however, none of these changes altered the final interpretation of the study. Of particular interest were lymphomas diagnosed in two 6,250 ppm males and one 25,000 ppm female. The PWG reviewed these and confirmed the diagnosis of malignant lymphoma in each case. The primary site of origin, however, could not be determined.

p16+/- Mice

Liver

The incidence of cytoplasmic vacuolization of periportal hepatocytes was reported to be increased in high dose males. Glass slides and/or digital images of the p16 male livers (control and high-dose) were reviewed by the PWG Chairperson and by several NIEHS pathologists. The outcome of this review was that there were no meaningful differences with respect to periportal hepatocyte cytoplasmic vacuolization in control versus high-dose male livers. The morphology of this change was noted to be consistent with normal glycogen in all cases. Based on this review it was recommended, and NIEHS pathologists agreed, that 8 CR control males be diagnosed as having minimal periportal hepatocyte cytoplasmic vacuolization and that all 9 CR high-dose males be diagnosed as having periportal hepatocyte cytoplasmic vacuolization (6 minimal and 3 mild). Like the controls, the morphology of this change was consistent with normal glycogen. Observed differences were attributed to biologic variation.

Controversial Sarcomas

There were a number of animals with controversial sarcomas affecting bone marrow (femur and skull), liver, ovary, spleen, lung, pancreas, meninges, gall bladder, and/or uterus. The SP tended to diagnose these as hemangiosarcomas when affecting marrow, theomas or thecal cell hyperplasia when affecting the ovary, and metastatic malignant theomas when affecting lung, uterus, or liver. The QAP and PWG Chairman diagnosed these all as histiocytic sarcomas. Upon review, the PWG agreed with the QAP and PWG Chairperson.

The bone marrow lesions were noted to be unusual in that there was often a dramatic hyperostotic (sclerotic) response to the tumor cells that began along the endosteum and gradually filled the marrow cavity. The reaction was noted to be similar to what occurs in some cases of osteomyelitis/bone injury, possibly representing an attempt by the animal to contain the tumor cells. However, in contrast to benign conditions, the intertrabecular areas of the reactive bone were clearly permeated by histiocytic tumor cells. Also, in contrast to what is generally expected with a malignant tumor in bone, there was no evidence of significant osteolysis/increased bone resorption. The end result in those cases with medullary hyperostosis/sclerosis, was a confounding mixture of histiocytic tumor cells intermingled with reactive host bone trabeculae. In some animals there was clear evidence that the bone formed was undergoing normal maturation, consistent with a reactive response. Marrow infarction was noted in one animal. Tumor cells of the same histiocytic morphology were present in other tissues (ovary, liver, spleen, lung, pancreas, and/or uterus) with no bone production at these sites, indicating that the tumor cells were not osteogenic and that the bone produced in the marrow was reactive as opposed to neoplastic.

SUMMARY

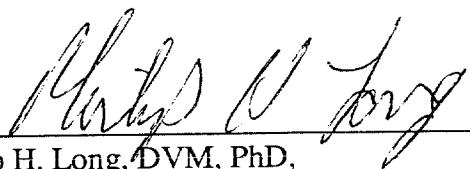
This review confirmed the opinion of the study pathologist that, under the conditions of this study, ASP was not carcinogenic when administered by dosed feed to hemizygous Tg.AC, heterozygous p53⁺⁻, or heterozygous p16⁺⁻ mice. This review also revealed a lack of any non-neoplastic treatment-related morphologic tissue effects. Differences in diagnoses/diagnostic terminology were minimal and did not alter the conclusion that there were no treatment-related neoplastic or non-neoplastic morphologic effects in any of the strains tested.

Post-PWG Action Items

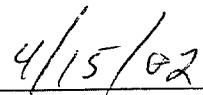
- Evaluate all tissues from Tg.AC control female #114 for the possibility of lymphoid/hematopoietic neoplasia. This was done and the animal was confirmed to be negative for neoplasia.

References

1. Goetz et al., *Lab Animal Sci* 48: 34-37, 1998.
2. J. F. Mahler, et. al., (1996). Spontaneous lesions in aging FVB/N mice. *Toxicol Pathol* 24:710-716.
3. J. F. Mahler JF, Flagler ND, Malarkey DE, Mann PC, Haseman JK, and Eastin W (1998). Spontaneous and chemically induced proliferative lesions in Tg.AC transgenic and p53-heterozygous mice. *Toxicol Pathol* 26; 501-511.
4. McLarrin GM (1982). Vacuoles in the fiber tracts of rat CNS tissues. *J Histotechnol* 5:171.
5. Pathology Working Group Peer Review of Proliferative Lesions in Subchronic Studies of Several Chemicals in p53⁺⁻ and Tg.AC Transgenic Mice (1997). EPL, Inc.
6. Wells GAH and Wells M (1989). Neuropil vacuolation in brain: a reproducible histological processing artifact. *J Comp Path* 101:355-362.



Philip H. Long, DVM, PhD,
Diplomate, ACVP
PWG Chairperson



Date

NATIONAL TOXICOLOGY PROGRAM

ASPARTAME Transgenic Model Evaluation II

CAS Number: 22839-47-0

Pathology Tables: Hemizygous Tg.AC, Heterozygous P53 +/-, and Heterozygous P16 +/- Mice

P03 – Incidence Rates of Non-Neoplastic Lesions by Anatomic Site (a)
Transgenic Model Evaluation II (Aspartame)

P05 – Incidence Rates of Neoplasms by Anatomic Site (Systemic Lesions Abridged) (a)
Transgenic Model Evaluation II (Aspartame)

P08 – Statistical Analysis of Primary Tumors
Transgenic Model Evaluation II (Aspartame)

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PEIRPT03
Date: 07/22/02
Time: 08:33:09

Facility: BIORELIANCE
Chemical CAS #: 22839-47-0
Lock Date: 07/20/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion
Page 1

NTP Experiment-Test: 99033-01
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:33:09

	MICE: TGAC (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
DISPOSITION SUMMARY							
Animals Initially In Study	15	15	15	15	15	15	15
Early Deaths							
Moribund Sacrifice	3	13	2	3	3	4	3
Natural Death	1	2		3	2	2	1
Survivors							
Terminal Sacrifice	11		10	9	9	9	11
Animals Examined Microscopically	15		15	15	15	15	15

ALIMENTARY SYSTEM

Gallbladder	(14)						
Inflammation, Chronic Active	1	(7%)					
Liver	(15)		(15)				
Infiltration Cellular, Focal, Lymphocyte	1	(7%)	1	(7%)			
Infiltration Cellular, Focal,							
Polymorphonuclear							
Inflammation, Acute, Focal	1	(7%)					
Inflammation, Chronic Active, Focal							
Necrosis							
Necrosis, Focal	1	(7%)					
Hepatocyte, Necrosis, Focal	1	(7%)					
Stomach, Forestomach							
Infiltration Cellular, Focal, Lymphocyte	(14)		(13)				
Muscularis, Inflammation, Acute, Focal							

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

Adrenal Cortex	(14)						
Accessory Adrenal Cortical Nodule	1	(7%)					
Atrophy	3	(21%)	2	(17%)	1	(8%)	4
Capsule, Inflammation, Acute, Focal							
Subcapsular, Hyperplasia, Focal	12	(86%)	6	(50%)	6	(46%)	5
Zona Reticularis, Vacuolization Cytoplasmic	12	(86%)	9	(75%)	6	(46%)	6
Pituitary Gland	(13)		(11)		(12)		9

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:33:09

	MICE:tgac (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
ENDOCRINE SYSTEM - CONT							
Cyst				2 (15%)			
Pars Intermedia, Hypertrophy							
						1 (9%)	
GENERAL BODY SYSTEM							
Tissue NOS				(2)			
Pigmentation				1 (50%)			
Abdominal, Fat, Necrosis, Focal				1 (50%)			
GENITAL SYSTEM							
Ovary				(15)			
Atrophy				2 (13%)			
Cyst, Focal							
Hemorrhage, Focal							
Uterus				(15)			
Cyst, Focal							
Hydrometra							
Endometrium, Hyperplasia, Cystic							
Vagina				10 (67%)			
Epithelium, Inflammation, Acute				(15)			
				1 (7%)			
HEMATOPOIETIC SYSTEM							
Lymph Node				(1)			
Renal, Hyperplasia				1 (100%)			
Lymph Node, Mandibular				(15)			
Hyperplasia				2 (13%)			
Inflammation, Acute, Focal							
Lymph Node, Mediastinal				(12)			
Hyperplasia				1 (8%)			
Spleen				(15)			
Accessory Spleen							
Hematopoietic Cell Proliferation							
Pigmentation							
Thymus				10 (67%)			
Atrophy, Diffuse				(15)			
Atrophy, Focal				10 (67%)			
Hyperplasia, Diffuse							

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
Date: 07/22/02
Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
INTEGUMENTARY SYSTEM						
Skin	(15)	(3)	(1)	(1)	(3)	(1) (33%)
MUSCULOSKELETAL SYSTEM						
None						
NERVOUS SYSTEM						
Brain	(15)	(12)	(13)	(13)	(14)	(1) (7%)
Abscess, Focal						
Inflammation, Acute, Focal						
Cerebellum, Corpus Callosum, Pons,						
Vacuolization Cytoplasmic, Focal						
Cortex, Cerebrum, Neuron, Necrosis						
Medulla, Vacuolization Cytoplasmic						
Pyramidal Cell, Hippocampus, Necrosis						
RESPIRATORY SYSTEM						
Lung	(15)	(14)	(14)	(15)	(14)	(14)
Hemorrhage, Focal						
Infiltration Cellular, Focal, Lymphocyte						
Inflammation, Chronic Active, Focal						
Alveolar Epithelium, Hyperplasia, Focal						
Perivascular, Infiltration Cellular,						
Lymphocyte						
SPECIAL SENSES SYSTEM						
Eye	(15)					
Retina, Atrophy	15 (100%)					
URINARY SYSTEM						
Kidney	(14)	(12)	(13)	(14)	(14)	(14)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE:tgac (FVB/N) HEMIZYGOS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
URINARY SYSTEM - CONT						
Infiltration Cellular, Focal, Lymphocyte	1 (7%)					
Inflammation, Acute, Focal		1 (7%)				
Nephropathy	1 (7%)		2 (17%)	1 (8%)		
Renal Tubule, Dilatation, Focal						

a Number of animals examined microscopically at site and number of animals with lesion

Report: PELRPT03
Date: 07/22/02
Time: 08:33:09

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PETRPT03
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE	50000 PPM
DISPOSITION SUMMARY	
Animals Initially In Study	15
Early Deaths	5
Natural Death	2
Moribund Sacrifice	
Survivors	8
Terminal Sacrifice	
Animals Examined Microscopically	15
ALIMENTARY SYSTEM	
Liver	(11)
Inflammation, Chronic Active, Focal	1 (9%)
Necrosis, Focal	3 (27%)
CARDIOVASCULAR SYSTEM	
None	
ENDOCRINE SYSTEM	
Adrenal Cortex	(10)
Atrophy	5 (50%)
Subcapsular, Hyperplasia, Focal	6 (60%)
Zona Reticularis, Vacuolization	
Cytoplasmic	6 (60%)
GENERAL BODY SYSTEM	
None	
GENITAL SYSTEM	
Uterus	(10)
Endometrium, Hyperplasia, Cystic	9 (90%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE 50000
PPM

HEMATOPOIETIC SYSTEM

Lymph Node, Mandibular Hyperplasia	(10) 1 (10%)
Spleen Hematopoietic Cell Proliferation	(11) 5 (45%)
Pigmentation	9 (82%)
Thymus Atrophy, Diffuse	(10) 2 (20%)
Atrophy, Focal	1 (10%)

INTEGUMENTARY SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

Brain Cortex, Cerebrum, Degeneration, Focal	(10) 1 (10%)
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RESPIRATORY SYSTEM

None

SPECIAL SENSES SYSTEM

Eye Retina, Atrophy	(10) 10 (100%)
Harderian Gland Inflammation, Chronic Active	(10) 1 (10%)

URINARY SYSTEM

Kidney

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PERIRPT03
Date: 07/22/02
Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS FEMALE	50000 PPM
<hr/>	
URINARY SYSTEM - CONT	
Mineralization, Focal	1 (10%)
Nephropathy	1 (10%)
Renal Tubule, Dilatation, Focal	1 (10%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PERIRPT03
 Date: 07/22/02
 Time: 08:33:09

	MICE: TGAC (FVB/N) HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
DISPOSITION SUMMARY							
Animals Initially In Study	15	15	15	15	15	15	15
Early Deaths	3	1	3	3	1	1	1
Natural Death	3	14	3	4	2	2	3
Moribund Sacrifice							
Survivors	9		12	8	12	11	
Terminal Sacrifice							
Animals Examined Microscopically	15		15	15	15	15	15

ALIMENTARY SYSTEM

Liver	(13)	(15)	(14)	(15)	(1)	(14)	(14)
Hematopoietic Cell Proliferation							
Inflammation, Acute, Focal	1 (8%)						
Stomach, Forestomach	(12)						
Epithelium, Hyperplasia	1 (8%)						

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

Adrenal Cortex	(12)	(15)	(13)	(14)	(15)	
Atrophy	10 (83%)	12 (80%)	8 (62%)	9 (64%)	8 (53%)	
Hypertrophy, Focal	10 (83%)	5 (33%)	5 (38%)	6 (43%)	7 (47%)	

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

Coagulating Gland	(12)	(1)
Cyst	1 (8%)	(1)
Preputial Gland		1 (100%)
Cyst		1 (100%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
GENITAL SYSTEM - CONT						
Prostate	(13)	(15) 1 (7%)	(15)	(15)	(15)	(15)
Inflammation, Acute, Focal						
Seminal Vesicle	(13)					
Dilatation						
Testes	(13)					
Cyst						
Cyst, Focal	1 (8%)					
Sertoli Cell, Germinal Epithelium,						
Degeneration	1 (8%)					
HEMATOPOIETIC SYSTEM						
Lymph Node, Mandibular	(12)	(15)	(13)	(14)	(14)	(14)
Hyperplasia	1 (8%)	2 (13%)				
Lymph Node, Mesenteric	(13)	(15)	(13)	2 (14%)		
Hyperplasia				1 (4%)		
Lymph Node, Mediastinal	(11)		1 (8%)			
Hyperplasia			(11)			
Spleen	(13)	(15)	(13)			
Hematopoietic Cell Proliferation	3 (23%)	3 (20%)	8 (62%)			
Pigmentation	9 (69%)	12 (80%)	8 (62%)			
Lymphoid Follicle, Depletion Cellular	(12)	1 (7%)	(12)			
Thymus	(12)	(14)	(12)			
Atrophy, Diffuse	1 (8%)	1 (8%)	1 (13)			
Atrophy, Focal	1 (8%)		1 (8%)			
INTEGUMENTARY SYSTEM						
Skin	(13)	(2)				
Control Epidermis, Hyperplasia, Focal						
MUSCULOSKELETAL SYSTEM						
NERVOUS SYSTEM	None					
None						

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PBIRPT03
Date: 07/22/02
Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
RESPIRATORY SYSTEM						
Lung Hemorrhage, Focal	(12)		(15)	(14)	(15)	(14)
SPECIAL SENSES SYSTEM						
Eye Retina, Atrophy	(12) 12 (100%)		(15)	(14)	(15)	(14)
URINARY SYSTEM						
Kidney Dilatation, Diffuse Nephropathy Renal Tubule, Dilatation, Diffuse Renal Tubule, Dilatation, Focal	(13) 1 (8%)		(15) 1 (8%)	(13) 1 (8%)	(15) 1 (8%)	(14) 1 (7%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PERIRPT03
Date: 07/22/02
Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS MALE	50000 PPM
DISPOSITION SUMMARY	
Animals Initially In Study	15
Early Deaths	
Moribund Sacrifice	4
Natural Death	1
Survivors	
Terminal Sacrifice	10
Animals Examined Microscopically	15
ALIMENTARY SYSTEM	
Liver	(14)
Hematopoietic Cell Proliferation	1 (7%)
Necrosis, Focal	1 (7%)
Stomach, Glandular	(14)
Inflammation, Acute	1 (7%)
CARDIOVASCULAR SYSTEM	
None	
ENDOCRINE SYSTEM	
Adrenal Cortex	(13)
Atrophy	6 (46%)
Hyper trophy, Focal	5 (38%)
Subcapsular, Hyperplasia, Focal	1 (8%)
GENERAL BODY SYSTEM	
None	
GENITAL SYSTEM	
Testes	(14)
Sertoli Cell, Germinal Epithelium, Degeneration	4 (29%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PETRPT03
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS MALE
50000
PPM

HEMATOPOIETIC SYSTEM

Bone Marrow	(14)
Hyperplasia	2 (14%)
Lymph Node, Mandibular	(14)
Hyperplasia	1 (7%)
Spleen	(14)
Hematopoietic Cell Proliferation	(14)
Pigmentation	4 (29%)
Thymus	11 (79%)
Atrophy, Focal	(12)
	2 (17%)

INTEGUMENTARY SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

Brain	(14)
Cortex, Cerebrum, Degeneration, Focal	1 (7%)

RESPIRATORY SYSTEM

Lung	(14)
Alveolar Epithelium, Hyperplasia, Focal	1 (7%)

SPECIAL SENSES SYSTEM

Eye	(14)
Retina, Atrophy	14 (100%)

URINARY SYSTEM

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PERIRPT03
Date: 07/22/02
Time: 08:33:09

MICE:tgac (FVB/N)	HEMIZYGOUS	MALE	50000 PPM
<hr/>			
URINARY SYSTEM - CONT			
Kidney	(14)		
Renal Tubule, Cyst	1	(7%)	
Renal Tubule, Dilatation, Diffuse	1	(7%)	

a Number of animals examined microscopically at site and number of animals with lesion

END OF REPORT

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PFRPT05
Date: 07/22/02
Time: 08:33:09

Facility: BIORELIANCE
Chemical CAS #: 22839-47-0
Lock Date: 07/20/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a) Report: PEIRPT05
 Study Type: 26-39 WEEKS Date: 07/22/02
 Route: DOSED FEED Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
DISPOSITION SUMMARY						
Animals Initially in Study	15	15	15	15	15	15
Early Deaths	3	13	2	3	4	3
Moribund Sacrifice	1	2	3	3	2	1
Natural Death						
Survivors	11	10	9	9	11	
Terminal Sacrifice						
Animals Examined Microscopically	15	15	15	15	15	
ALIMENTARY SYSTEM						
Liver	(15)	(15)	(14)	(15)	(1)	(14)
Sarcoma, Stromal, Metastatic, Uterus	(15)	(15)	(1)	(1)	(1)	
Salivary Glands						
Duct, Carcinoma						
Stomach, Forestomach	(14)	(13)	(13)	(15)	(1)	(14)
Squamous Cell Papilloma	2 (14%)	6 (46%)	1 (8%)	7 (47%)	3 (21%)	
Squamous Cell Papilloma, Multiple	2 (14%)	3 (23%)	3 (23%)	4 (29%)	4 (29%)	
Tooth	(4)	(4)	(2)	(5)	(5)	
Odontoma	3 (75%)	4 (100%)	2 (100%)	5 (100%)	5 (100%)	
CARDIOVASCULAR SYSTEM						
None						
ENDOCRINE SYSTEM						
Pituitary Gland	(13)	(11)	(12)	(10)	(11)	
GENERAL BODY SYSTEM						
None						

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

Report: PEIRPT05
 Date: 07/22/02
 Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
GENITAL SYSTEM						
Ovary			(15)	(15)	(14)	(14)
Uterus			(15)	(13)	(12)	(14)
Sarcoma Stromal					1 (8%)	
HEMATOPOIETIC SYSTEM						
Lymph Node			(1)		(1)	
Pancreatic, Sarcoma Stromal, Metastatic,				1 (100%)		
Uterus				(12)	(12)	(11)
Lymph Node, Mediastinal					1 (8%)	
Carcinoma, Metastatic, Salivary Glands			(15)	(14)	(12)	(14)
Spleen						
INTREGUMENTARY SYSTEM						
Skin			(15)	(3)	(1)	(3)
Squamous Cell Papilloma				2 (67%)	1 (100%)	
Vulva, Squamous Cell Papilloma			1 (7%)	1 (33%)	2 (67%)	
MUSCULOSKELETAL SYSTEM						
None						
NERVOUS SYSTEM						
Brain			(15)	(12)	(13)	(14)
RESPIRATORY SYSTEM						
Lung			(15)	(14)	(15)	(14)
Alveolar/Bronchiolar Adenoma			1 (7%)		1 (7%)	
Carcinoma, Metastatic, Salivary Glands						

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
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SPECIAL SENSES SYSTEM

None

URINARY SYSTEM

Kidney

(14) (12) (13) (14) (14)

SYSTEMIC LESIONS

Multiple Organs * (15)
 Leukemia Erythrocytic 1 (7%) 3 (20%) 1 (7%)

* Number of animals with any tissue examined microscopically

Report: PEIRPT05
 Date: 07/22/02
 Time: 08:33:09

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

Report: PEIRPT05
 Date: 07/22/02
 Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS FEMALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
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TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	7	12	8	11	11	11
Total Primary Neoplasms	10	19	8	14	14	14
Total Animals with Benign Neoplasms	7	12	7	9	11	11
Total Benign Neoplasms	9	16	7	12	14	14
Total Animals with Malignant Neoplasms	1	3	1	2	2	2
Total Malignant Neoplasms	1	3	1	2	2	2
Total Animals with Metastatic Neoplasms				2	2	2
Total Metastatic Neoplasm				4	4	4
Total Animals with Malignant Neoplasms						
Uncertain Primary Site						
Total Animals with Neoplasms Uncertain-						
Benign or Malignant						
Total Uncertain Neoplasms						

a Number of animals examined microscopically at site and number of animals with lesion
 b Primary tumors: all tumors except metastatic tumors

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE 50000
PPM

DISPOSITION SUMMARY

Animals Initially in Study	15
Early Deaths	
Natural Death	5
Moribund Sacrifice	2
Survivors	
Terminal Sacrifice	8
Animals Examined Microscopically	15

ALIMENTARY SYSTEM

Liver	(11)
Salivary Glands	(11)
Duct, Carcinoma	1 (9%)
Stomach, Forestomach	(10)
Squamous Cell Papilloma	5 (50%)
Tooth	(1)
Odontoma	1 (100%)

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

None

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

None

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE	50000 PPM	(11)
HEMATOPOIETIC SYSTEM		
Spleen		
INTEGUMENTARY SYSTEM		
None		
MUSCULOSKELETAL SYSTEM		
None		
NERVOUS SYSTEM		
None		
RESPIRATORY SYSTEM		
None		
SPECIAL SENSES SYSTEM		
None		
URINARY SYSTEM		
None		
SYSTEMIC LESIONS		
Multiple Organs	* (15)	
Leukemia Erythrocytic	1 (7%)	

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS FEMALE

50000
PPM

TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	
Total Primary Neoplasms	7
Total Animals with Benign Neoplasms	8
Total Benign Neoplasms	5
Total Animals with Malignant Neoplasms	6
Total Malignant Neoplasms	2
Total Animals with Metastatic Neoplasms	2
Total Metastatic Neoplasm	2
Total Animals with Malignant Neoplasms	2
Uncertain Primary Site	
Total Animals with Neoplasms Uncertain-	
Benign or Malignant	
Total Uncertain Neoplasms	

a Number of animals examined microscopically at site and number of animals with lesion

b Primary tumors: all tumors except metastatic tumors

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

Report: PETRPT05
 Date: 07/22/02
 Time: 08:33:09

MICE:TGAC (FVB/N)	HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
DISPOSITION SUMMARY							
Animals Initially in Study							
Early Deaths		15	15	15	15	15	15
Natural Death		3	1	3	1	1	1
Moribund Sacrifice		3	4	3	2	2	3
Survivors		9	12	8	12	11	11
Terminal Sacrifice							
Animals Examined Microscopically		15	15	15	15	15	15
ALIMENTARY SYSTEM							
Liver		(13)	(15)	(14)	(15)	(14)	(14)
Salivary Glands		(13)	(2)	(2)	(2)	(2)	(2)
Duct, Carcinoma			2 (100%)			1 (50%)	
Stomach, Forestomach		(12)	(13)	(13)	(14)	(14)	(14)
Squamous Cell Papilloma		4 (33%)	1 (7%)	1 (8%)	3 (21%)	4 (29%)	
Squamous Cell Papilloma, Multiple		4 (33%)	4 (27%)	1 (8%)	2 (14%)	2 (14%)	
Tooth		(4)	(4)	(2)	(2)	(2)	(2)
Odontogenic Tumor		2 (50%)	4 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)
CARDIOVASCULAR SYSTEM							
None							
ENDOCRINE SYSTEM							
Adrenal Cortex		(12)	(15)	(13)	(14)	(15)	
GENERAL BODY SYSTEM							
None							

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a) Report: PEIRPT05
 Study Type: 26-39 WEEKS Date: 07/22/02
 Route: DOSED FEED Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
GENITAL SYSTEM						
None						
LYMPHOPOIETIC SYSTEM						
Lymph Node, Mediastinal						
	(11)	(13)	(11)	(10)	(14)	
	(13)	(15)	(13)	(15)	(14)	
	(12)	(14)	(12)	(13)	(14)	
INTEGUMENTARY SYSTEM						
Skin						
Squamous Cell Papilloma						
	(13)	(2)	(1)			
		2 (100%)	1			
MUSCULOSKELETAL SYSTEM						
None						
NERVOUS SYSTEM						
None						
RESPIRATORY SYSTEM						
Lung						
Alveolar/Bronchiolar Adenoma						
	(12)	(15)	(14) 2 (14%)	(15) 1 (7%)	(14) 2 (14%)	
SPECIAL SENSES SYSTEM						
Zymbal's Gland						
Carcinoma						
	(12)					
			(1)			
			1	(100%)		

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

TRANSENTRIC MODEL EVALUATION II(ASPARTAME)
 Report: PEIRPT05
 Date: 07/22/02
 Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
URINARY SYSTEM						
Kidney						
(13)			(15)	(13)	(15)	(14)
SYSTEMIC LESIONS						
Multiple Organs	*	(15)	*	(15)	*	(15)
Leukemia	1	(7%)	1	(7%)	2	(13%)
Lymphoma			1	(7%)		
Malignant						

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

Report: PEIRPT05
 Date: 07/22/02
 Time: 08:33:09

MICE: TGAC (FVB/N) HEMIZYGOUS MALE	VEHICLE CONTROL	TPA CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM
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TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	10	9	7	8	10	11
Total Primary Neoplasms	11	11	10	10	10	13
Total Animals with Benign Neoplasms	8	6	5	8		
Total Benign Neoplasms	8	7	4	6		
Total Animals with Malignant Neoplasms	1	4	2	2		
Total Malignant Neoplasms	1	4	2	2		
Total Animals with Metastatic Neoplasms						
Total Metastatic Neoplasm						
Total Animals with Malignant Neoplasms						
Uncertain Primary Site						
Total Animals with Neoplasms Uncertain-						
Benign or Malignant	2	4	2	2		
Total Uncertain Neoplasms	2	4	2	2		

a Number of animals examined microscopically at site and number of animals with lesion
 b Primary tumors: all tumors except metastatic tumors

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS MALE 50000 PPM

DISPOSITION SUMMARY

Animals Initially in Study	15
Early Deaths	
Moribund Sacrifice	4
Natural Death	1
Survivors	10
Terminal Sacrifice	
Animals Examined Microscopically	15

ALIMENTARY SYSTEM

Liver	(14)
Salivary Glands	(14)
Duct, Carcinoma	1 (7%)
Stomach, Forestomach	(14)
Squamous Cell Papilloma	5 (36%)
Squamous Cell Papilloma, Multiple	1 (7%)
Tooth	(6)
Odontogenic Tumor	5 (83%)
Odontoma	1 (17%)

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

None

GENERAL BODY SYSTEM

None

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a) Report: PEIRPT05
Study Type: 26-39 WEEKS Date: 07/22/02
Route: DOSED FEED Time: 08:33:09
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

MICE:TGAC (FVB/N) HEMIZYGOUS MALE 50000 PPM

GENITAL SYSTEM

None

HEMATOPOIETIC SYSTEM

Lymph Node, Mandibular (14)
Lymph Node, Mesenteric (14)
Lymph Node, Mediastinal (13)
Thymus (12)

INTEGUMENTARY SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

None

RESPIRATORY SYSTEM

Lung (14)
Alveolar/Bronchiolar Adenoma 2 (14%)

SPECIAL SENSES SYSTEM

Harderian Gland (14)
Adenoma 1 (7%)

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS MALE 50000 PPM

URINARY SYSTEM

None

SYSTEMIC LESIONS

Multiple Organs *
Lymphoma Malignant 1 (15)
1 (7%)

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-01 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:33:09

MICE:TGAC (FVB/N) HEMIZYGOUS MALE

50000
PPM

TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	11
Total Primary Neoplasms	17
Total Animals with Benign Neoplasms	8
Total Benign Neoplasms	10
Total Animals with Malignant Neoplasms	2
Total Malignant Neoplasms	2
Total Animals with Metastatic Neoplasms	2
Total Metastatic Neoplasm	2
Total Animals with Malignant Neoplasms	2
Uncertain Primary Site	2
Total Animals with Neoplasms Uncertain-	5
Benign or Malignant	5
Total Uncertain Neoplasms	5

a Number of animals examined microscopically at site and number of animals with lesion

b Primary tumors: all tumors except metastatic tumors

END OF REPORT

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 01
TEST TYPE: 26-39 WEEKS
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDA

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

REPORT: PEIRFT08
DATE: 07/22/02
TIME: 08:33:15
PAGE: 1
NTP C#: C99013
CAS: 22839-47-0

REASONS FOR REMOVAL: ALL

REMOVAL DATE RANGE: ALL
TREATMENT GROUPS: INCLUDE ALL

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 01
TEST TYPE: 26-39 WEEKS
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDIA
Mice (TG.AC HETEROZYGOUS TRANSGENIC)

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II (ASPARTAME)
REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:33:15
NTP C#: C99033
CAS: 22839-47-0

FOR ALL DOSES THE TUMOR RATES IN THE FOLLOWING TISSUES/ORGANS ARE
BASED ON NUMBER OF TISSUES EXAMINED. IN OTHER TISSUES/ORGANS RATES
ARE BASED ON THE NUMBER OF ANIMALS NECROPSIED.

ROUTE : DOSED FEED
Lung
Salivary Glands

NTP LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 01
TEST TYPE: 26-39 WEEKS
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDIA

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:33:15
NTP C#: C99033
CAS: 22839-47-0

SUMMARY OF STATISTICALLY SIGNIFICANT ($P \leq .05$) RESULTS
IN THE ANALYSIS OF TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Male Mice		Morphology	Male Mice	
Organ			Organ	
Salivary Glands		Carcinoma	Stomach	Papilloma
Tooth		Odontogenic Tumor	Forestomach	Leukemia: Erythrocytic
All Organs		Odontoma		Benign Tumors
		Benign Tumors		Malignant Tumors
		Malignant Tumors		Malignant and Benign Tumors
Female Mice		Morphology	Female Mice	
Organ			Organ	
Salivary Glands		Carcinoma	Stomach	Papilloma
Stomach, Forestomach		Squamous Cell	Forestomach	Leukemia: Erythrocytic
All Organs		Benign Tumors		Benign Tumors
		Malignant Tumors		Malignant and Benign Tumors

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice (TG.AC HETEROZYGOUS TRANSGENIC)

EXPERIMENT: 99033 TEST: 01
TRANSGENIC MODEL EVALUATION III (ASPARTAME)

Page 1
Terminal Sacrifice at 40 weeks

Dose	VEHICLE CONTROL	3125 PPM PPM	6250 PPM PPM	Males 12500 PPM	Females 25000 PPM	Females 25000 PPM	Females 50000 PPM
Lung Alveolar/Bronchiolar Adenoma							
TUMOR RATES							
OVERALL (a)							
POLY -3 RATE (b)	0/11.90	0/15 (0%)	2/14 (14%)	1/15 (7%)	2/14 (14%)	2/14 (14%)	2/14 (14%)
POLY -3 PERCENT (g)	0.0%	0/14.31	2/10.17	1/13.78	2/12.66	2/11.92	2/11.92
TERMINAL (d)	0/9 (0%)	0/8 (0%)	19.7%	7.3%	15.8%	16.8%	16.8%
FIRST INCIDENCE	---	0/12 (0%)	2/8 (25%)	1/12 (8%)	2/11 (18%)	2/10 (20%)	2/10 (20%)
STATISTICAL TESTS							
LIFE TABLE							
POLY 3	P=0.128	(e)	P=0.207	P=0.557	P=0.280	P=0.257	P=0.257
POLY 1.5	P=0.096	(e)	P=0.194	P=0.529	P=0.243	P=0.229	P=0.229
POLY 6	P=0.109	(e)	P=0.217	P=0.535	P=0.251	P=0.243	P=0.243
LOGISTIC REGRESSION	P=0.085	(e)	P=0.179	P=0.523	P=0.236	P=0.218	P=0.218
COCH-ARM / FISHERS	(e)	P=0.132	P=0.207	P=0.557	P=0.280	P=0.257	P=0.257
Dose							
VEHICLE CONTROL							
Lung Alveolar/Bronchiolar Adenoma							
TUMOR RATES							
OVERALL (a)							
POLY -3 RATE (b)	1/15 (7%)	0/14 (0%)	0/14 (0%)	0/15 (0%)	0/14 (0%)	0/10 (0%)	0/10 (0%)
POLY -3 PERCENT (g)	7.7%	0/13.08	0/12.09	0/10.85	0/13.80	0/9.24	0/9.24
TERMINAL (d)	1/11 (9%)	0/8 (0%)	0/8 (0%)	0/9 (0%)	0/9 (0%)	0/8 (0%)	0/8 (0%)
FIRST INCIDENCE	275 (T)	---	---	---	---	---	---
STATISTICAL TESTS							
LIFE TABLE							
POLY 3	P=0.437N	(e)	P=0.519N	P=0.540N	P=0.540N	P=0.564N	P=0.564N
POLY 1.5	P=0.426N	P=0.516N	P=0.553N	P=0.537N	P=0.489N	P=0.569N	P=0.569N
POLY 6	P=0.433N	P=0.513N	P=0.545N	P=0.526N	P=0.497N	P=0.572N	P=0.572N
LOGISTIC REGRESSION	P=0.419N	P=0.520N	P=0.557N	P=0.542N	P=0.483N	P=0.567N	P=0.567N
COCH-ARM / FISHERS	(e)	P=0.437N	(e)	(e)	(e)	(e)	(e)

Date: 07/22/02 EXPERIMENT: 99033 TEST: 01
 Statistical Analysis of Primary Tumors in Mice(TG.AC HETEROZOOGOUS TRANSGENIC)
 - Terminal Sacrifice at 40 weeks

Dose	VEHICLE CONTROL	Males		Females		
		6250 PPM PPM	12500 PPM PPM	6250 PPM PPM	12500 PPM PPM	
Salivary Glands Carcinoma						
TUMOR RATES						
OVERALL (a)		0/13 (0%)	0/0 (0%)	2/2 (100%)	0/0 (0%)	
POLY-3 RATE (b)		0/11.92	0/0.00	2/2.00	0/0.00	
POLY-3 PERCENT (g)		0.0%	0.0%	100.0%	0.0%	
TERMINAL (d)		0/9 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	
FIRST INCIDENCE		---	---	138	138	
STATISTICAL TESTS						
LIFE TABLE		P=0.366 (e)	P=0.190 (e)	P=0.473 (e)	P=0.483 (e)	
POLY 3		(e)	P<0.001 ** (e)	P=0.068 (e)	P=0.501 (e)	
POLY 1, 5		(e)	P<0.001 ** (e)	P=0.074 (e)	P=0.510 (e)	
POLY 6		(e)	P<0.001 ** (e)	P=0.058 (e)	P=0.491 (e)	
LOGISTIC REGRESSION		P=0.628 (e)	P=0.030 * (e)	P=0.269 (e)	P=0.495 (e)	
COCH-ARM / FISHERS		P=0.514N (e)	P=0.010 * (e)	P=0.133 (e)	P=0.519 (e)	
Salivary Glands Carcinoma						
TUMOR RATES						
OVERALL (a)		0/15 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)	
POLY-3 RATE (b)		0/13.08	0/0.00	0/0.00	1/1.00%	
POLY-3 PERCENT (g)		0.0%	0.0%	0.0%	100.0%	
TERMINAL (d)		0/11 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	
FIRST INCIDENCE		---	---	---	97	
STATISTICAL TESTS						
LIFE TABLE		P=0.180 (e)	(e)	(e)	P=0.390 (e)	
POLY 3		(e)	(e)	(e)	P<0.001 ** (e)	
POLY 1, 5		(e)	(e)	(e)	P<0.001 ** (e)	
POLY 6		(e)	(e)	(e)	P<0.001 ** (e)	
LOGISTIC REGRESSION		P=0.340 (e)	(e)	(e)	P=0.433 (e)	
COCH-ARM / FISHERS		P=0.401 (e)	(e)	(e)	P=0.423 (e)	

Date: 07/22/02

Statistical Analysis of Primary Tumors in Mice(TG.AC HETEROZYGOUS TRANSGENIC)
Terminal Sacrifice at 40 weeksEXPERIMENT: 99033 TEST: 01
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

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TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males 12500 PPM	25000 PPM	Females 12500 PPM	25000 PPM
Skin Squamous Cell Papilloma							
TUMOR RATES							
OVERALL (a)							
POLY-3 RATE (b)		0/30 (0%)	2/15 (13%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	0/15 (0%)
POLY-3 PERCENT (g)		0/14.87	2/14.31	0/10.20	0/13.78	1/12.70	0/12.06
TERMINAL (d)		0.0%	14.0%	0.0%	0.0%	7.9%	0.0%
FIRST INCIDENCE		0/9 (0%)	2/12 (17%)	0/8 (0%)	0/12 (0%)	1/11 (9%)	0/10 (0%)
STATISTICAL TESTS							
LIFE TABLE							
POLY 3		P=0.300	(e)			P=0.540	(e)
POLY 1.5		P=0.220	(e)			P=0.467	(e)
POLY 6		P=0.167	(e)			P=0.428	(e)
LOGISTIC REGRESSION		P=0.260	(e)			P=0.495	(e)
COCH-ARM / FISHERS		P=0.327N	(e)			P=0.540	(e)
		(e)	P=0.300	(e)		P=0.333	(e)
		P=0.531N	P=0.106				
Skin Squamous Cell Papilloma							
TUMOR RATES							
OVERALL (a)							
POLY-3 RATE (b)		1/30 (3%)	3/15 (20%)	1/15 (7%)	0/15 (0%)	2/15 (13%)	0/15 (0%)
POLY-3 PERCENT (g)		1/14.98	3/12.74	1/10.06	0/10.85	2/13.80	0/9.98
TERMINAL (d)		6.7%	23.5%	9.9%	0.0%	14.5%	0.0%
FIRST INCIDENCE		1/11 (9%)	2/10 (20%)	1/9 (11%)	0/9 (0%)	2/11 (18%)	0/8 (0%)
STATISTICAL TESTS							
LIFE TABLE							
POLY 3		P=0.264	(e)			P=0.540N	(e)
POLY 1.5		P=0.213N	P=0.231			P=0.567N	(e)
POLY 6		P=0.249N	P=0.173			P=0.591N	(e)
LOGISTIC REGRESSION		P=0.193N	P=0.272			P=0.550N	(e)
COCH-ARM / FISHERS		P=0.257N	P=0.201			P=0.500	(e)
		P=0.332N	P=0.101			P=0.667N	(e)
						P=0.254	(e)

Date: 07/22/02 EXPERIMENT: 99033 TEST: 01
 Statistical Analysis of Primary Tumors in Mice (TG.AC HETEROZYGOUS TRANSGENIC)
 Terminal Sacrifice at 40 weeks

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TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Dose	VEHICLE CONTROL	Males		Females		
		3125 PPM PPM	6250 PPM PPM	12500 PPM PPM	25000 PPM PPM	
Stomach, Forestomach Squamous Cell Papilloma						
STATISTICAL TESTS						
TUMOR RATES	#	#	#	#	#	
OVERALL (a)	8/30 (27%)	5/15 (33%)	2/15 (13%)	5/15 (33%)	6/15 (40%)	
POLY-3 RATE (b)	8/14.97	5/14.31	2/10.23	5/13.81	6/12.70	
POLY-3 PERCENT (g)	53.4%	34.9%	19.6%	36.2%	47.3%	
TERMINAL (d)	5/9 (56%)	5/12 (42%)	1/8 (13%)	4/12 (33%)	5/10 (50%)	
FIRST INCIDENCE	274 (T)	271	274 (T)	271	180	
STATISTICAL TESTS						
LIFE TABLE	P=0.448	P=0.100N	P=0.068N	P=0.122N	P=0.241N	
POLY 3	P=0.296	P=0.255N	P=0.079N	P=0.282N	P=0.524N	
POLY 1.5	P=0.261	P=0.452N	P=0.136N	P=0.472N	P=0.587	
POLY 6	P=0.306	P=0.154N	P=0.052N	P=0.181N	P=0.385N	
LOGISTIC REGRESSION	P=0.350	P=0.115N	P=0.056N	P=0.150N	P=0.349N	
COCH-ARM / FISHERS	P=0.142	P=0.447	P=0.269N	P=0.447	P=0.282	
Dose	VEHICLE CONTROL	3125 PPM PPM	6250 PPM PPM	12500 PPM PPM	25000 PPM PPM	
Stomach, Forestomach Squamous Cell Papilloma						
STATISTICAL TESTS						
TUMOR RATES	#	#	#	#	#	
OVERALL (a)	4/30 (13%)	9/15 (60%)	4/15 (27%)	7/15 (47%)	7/15 (47%)	
POLY-3 RATE (b)	4/14.98	9/12.82	4/10.06	7/11.59	7/13.94	
POLY-3 PERCENT (g)	26.7%	70.2%	39.8%	60.4%	50.2%	
TERMINAL (d)	4/11 (36%)	7/10 (70%)	4/9 (44%)	5/9 (56%)	5/11 (46%)	
FIRST INCIDENCE	275 (T)	192	275 (T)	184	184	
STATISTICAL TESTS						
LIFE TABLE	P=0.445	P=0.048 *	P=0.536	P=0.123	P=0.242	
POLY 3	P=0.522N	P=0.016 *	P=0.397	P=0.171	P=0.253	
POLY 1.5	P=0.464	P=0.004 **	P=0.324	P=0.074	P=0.180	
POLY 6	P=0.428N	P=0.033 *	P=0.453	P=0.113	P=0.317	
LOGISTIC REGRESSION	P=0.457	P=0.026 *	P=0.536	P=0.077	P=0.268	
COCH-ARM / FISHERS	P=0.252	P=0.002 **	P=0.241	P=0.020 *	P=0.020 *	

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice(TG.AC HETEROZYGOUS TRANSGENIC)

EXPERIMENT: 99033 TEST: 01
Terminal Sacrifice at 40 weeks - TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males	12500 PPM	25000 PPM	Females	50000 PPM
Tooth Odontogenic Tumor								
TUMOR RATES								
OVERALL (a)								
POLY-3 RATE (b)		2/30 (7%)	4/15 (27%)		2/15 (13%)	2/15 (13%)		5/15 (33%)
POLY-3 PERCENT (g)		12.6%	26.7% 0/9 (0%)		19.6%	21.3-81 14.5% 1/12 (8%)		5/13.42 37.3% 1/11 (9%)
TERMINAL (d)								
FIRST INCIDENCE		76	198	271	271	261	180	2/10 (20%)
STATISTICAL TESTS								
LIFE TABLE		P=0.153	P=0.348		P=0.566	P=0.676		P=0.643
POLY 3		P=0.147	P=0.296		P=0.530	P=0.652		P=0.624
POLY 1.5		P=0.114	P=0.196		P=0.489	P=0.578		P=0.551
POLY 6		P=0.170	P=0.377		P=0.560	P=0.696		P=0.672
LOGISTIC REGRESSION		P=0.072	P=0.079		P=0.471	P=0.52		P=0.457
COCH-ARM / FISHERS		P=0.054	P=0.085		P=0.407	P=0.407		P=0.32 *
Tooth Odontogenic Tumor								
TUMOR RATES								
OVERALL (a)								
POLY-3 RATE (b)		0/30 (0%)	0/15 (0%)		0/15 (0%)	0/15 (0%)		0/15 (0%)
POLY-3 PERCENT (g)		0/14.98	0/12.12		0/10.06	0/10.85		0/13.80
TERMINAL (d)		0.0%	0.0%		0.0%	0.0%		0.0%
FIRST INCIDENCE		0/11 (0%)	0/9 (0%)		0/9 (0%)	0/11 (0%)		0/8 (0%)
STATISTICAL TESTS								
LIFE TABLE		(e)	(e)		(e)	(e)		(e)
POLY 3		(e)	(e)		(e)	(e)		(e)
POLY 1.5		(e)	(e)		(e)	(e)		(e)
POLY 6		(e)	(e)		(e)	(e)		(e)
LOGISTIC REGRESSION		(e)	(e)		(e)	(e)		(e)
COCH-ARM / FISHERS		(e)	(e)		(e)	(e)		(e)

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice (TG AC HETEROZOYGUS TRANSGENIC)

EXPERIMENT: 99033 TEST: 01
Terminal Sacrifice at 40 weeks

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TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Dose	VEHICLE CONTROL		Males		Females	
	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM	
Tooth Odontoma						
STATISTICAL TESTS						
LIFE TABLE	P=0.105	(e)	#	#	#	P=0.473
POLY 3	P=0.092	(e)				P=0.469
POLY 1.5	P=0.089	(e)				P=0.431
POLY 6	P=0.094	(e)				P=0.494
LOGISTIC REGRESSION	P=0.037 *	(e)				P=0.255
COCH-ARM / FISHERS	P=0.079	(e)				P=0.333
STATISTICAL TESTS						
LIFE TABLE	P=0.30	(0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	1/15 (7%)
OVERALL (a)	0/14.87		0/14.31	0/10.20	0/13.78	1/12.78
POLY-3 RATE (b)	0.0%		0.0%	0.0%	0.0%	7.8%
POLY-3 PERCENT (g)	0/9 (0%)		0/12 (0%)	0/12 (0%)	0/11 (0%)	0/10 (0%)
TERMINAL (d)	---		---	---	---	180
FIRST INCIDENCE	---		---	---	---	---
Tooth Odontoma						
TUMOR RATES	#	#	#	#	#	#
OVERALL (a)	3/30 (10%)	4/15 (27%)	2/15 (13%)	5/15 (33%)	5/15 (33%)	1/15 (7%)
POLY-3 RATE (b)	3/16.59	4/12.74	2/11.25	5/13.16	5/14.00	1/10.68
POLY-3 PERCENT (g)	18.4%	31.4%	17.8%	38.0%	35.7%	9.4%
TERMINAL (d)	0/11 (0%)	2/10 (20%)	0/9 (0%)	1/9 (11%)	2/11 (18%)	0/8 (0%)
FIRST INCIDENCE	109	206	200	165	267	184
STATISTICAL TESTS						
LIFE TABLE	P=0.360N	(P=0.416)	(P=0.651N)	(P=0.229)	(P=0.335)	P=0.477N
POLY 3	P=0.352N	(P=0.340)	(P=0.688N)	(P=0.239)	(P=0.239)	P=0.470N
POLY 1.5	P=0.398N	(P=0.268)	(P=0.647)	(P=0.153)	(P=0.153)	P=0.511N
POLY 6	P=0.331N	(P=0.383)	(P=0.646N)	(P=0.259)	(P=0.304)	P=0.445N
LOGISTIC REGRESSION	P=0.469N	(P=0.214)	(P=0.559)	(P=0.055)	(P=0.136)	P=0.594N
COCH-ARM / FISHERS	P=0.489N	(P=0.154)	(P=0.547)	(P=0.068)	(P=0.068)	P=0.593N

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice (TG.AC HETEROZYGOUS TRANSGENIC)

EXPERIMENT: 99033 TEST: 01
Terminal Sacrifice at 40 weeks

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TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males 12500 PPM	Males 25000 PPM	Females 12500 PPM	Females 25000 PPM
All Organs							
Leukemia: Erythrocytic							
TUMOR RATES							
OVERALL (a)							
POLY-3 RATE (b)	1/30 (3%)	0/15 (0%)	1/15 (7%)	2/15 (13%)	0/15 (0%)	0/15 (0%)	
POLY 3 PERCENT (g)	1/15.50	0/14.31	1/10.83	2/14.97	0/12.70	0/12.06	
TERMINAL (d)	6.5%	0.0%	9.2%	13.4*	0.0%	0.0%	
FIRST INCIDENCE	0/9 (0%)	0/12 (0%)	0/8 (0%)	0/12 (0%)	0/11 (0%)	0/10 (0%)	
STATISTICAL TESTS							
LIFE TABLE	P=0.296N	P=0.500N	P=0.693	P=0.526	P=0.529N	P=0.545N	
POLY 3	P=0.314N	P=0.516N	P=0.687	P=0.487	P=0.541N	P=0.552N	
POLY 1.5	P=0.321N	P=0.557N	P=0.656	P=0.408	P=0.576N	P=0.580N	
POLY 6	P=0.315N	P=0.491N	P=0.708	P=0.538	P=0.519N	P=0.536N	
LOGISTIC REGRESSION	P=0.455N	P=0.757N	P=0.591	P=0.141	P=0.690N	P=0.693N	
COCH-ARM / FISHERS	P=0.363N	P=0.667N	P=0.561	P=0.254	P=0.667N	P=0.667N	
All Organs							
Leukemia: Erythrocytic							
TUMOR RATES							
OVERALL (a)							
POLY-3 RATE (b)	1/30 (3%)	3/15 (20%)	1/15 (7%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	
POLY-3 PERCENT (g)	1/15.92	3/13.98	1/10.91	0/10.85	0/13.80	1/10.50	
TERMINAL (d)	6.3%	21.5%	9.2%	0.0%	0.0%	9.5%	
FIRST INCIDENCE	0/11 (0%)	0/10 (0%)	0/9 (0%)	0/9 (0%)	0/11 (0%)	0/8 (0%)	
STATISTICAL TESTS							
LIFE TABLE	P=0.393N	P=0.232	P=0.627	P=0.623N	P=0.623N	P=0.644	
POLY 3	P=0.275N	P=0.245	P=0.682	P=0.579N	P=0.529N	P=0.673	
POLY 1.5	P=0.328N	P=0.179	P=0.650	P=0.599N	P=0.569N	P=0.643	
POLY 6	P=0.246N	P=0.297	P=0.703	P=0.566N	P=0.504N	P=0.695	
LOGISTIC REGRESSION	P=0.493N	P=0.028 *	P=0.579	P=0.830N	P=0.736N	P=0.564	
COCH-ARM / FISHERS	P=0.451N	P=0.101	P=0.561	P=0.667N	P=0.667N	P=0.561	

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice (TG.AC HETEROZOYGOUS TRANSGENIC)

EXPERIMENT: 99033 TEST: 01
Terminal Sacrifice at 40 weeks

Dose	All Organs		Males		Females	
	VEHICLE	CONTROL	3125 PPM	6250 PPM	25000 PPM	50000 PPM
TUMOR RATES	#	#	#	#	#	#
OVERALL (a)	8/30 (27%)	6/15 (40%)	3/15 (20%)	5/15 (33%)	8/15 (53%)	8/15 (53%)
POLY-3 RATE (b)	8/14.97	6/14.31	3/10.23	5/13.81	8/12.70	8/12.78
POLY-3 PERCENT (g)	53.4%	41.9%	29.3%	36.2%	63.0%	62.6%
TERMINAL (d)	5/9 (55%)	6/12 (50%)	2/8 (25%)	4/12 (33%)	8/11 (73%)	7/10 (70%)
FIRST INCIDENCE	271	274 (T)	271	274 (T)	180	180
STATISTICAL TESTS						
LIFE TABLE	P=0.181	P=0.163N	P=0.122N	P=0.475N	P=0.577N	
POLY 3	P=0.080	P=0.397N	P=0.197N	P=0.282N	P=0.448	P=0.456
POLY 1.5	P=0.065	P=0.618N	P=0.291N	P=0.472N	P=0.242	P=0.257
POLY 6	P=0.085	P=0.259N	P=0.144N	P=0.181N	P=0.613	P=0.610
LOGISTIC REGRESSION	P=0.101	P=0.199N	P=0.137N	P=0.150N	P=0.649	P=0.498
COCH-ARM / FISHERS	P=0.026 *	P=0.282	P=0.460N	P=0.447	P=0.077	P=0.077

All Organs
Benign Tumors

Dose	All Organs		Males		Females	
	VEHICLE	CONTROL	3125 PPM	6250 PPM	25000 PPM	50000 PPM
TUMOR RATES	#	#	#	#	#	#
OVERALL (a)	7/30 (23%)	12/15 (80%)	7/15 (47%)	9/15 (60%)	11/15 (73%)	5/15 (33%)
POLY-3 RATE (b)	7/16.59	12/14.03	7/11.25	9/13.16	11/14.00	5/10.68
POLY-3 PERCENT (g)	42.2%	85.6%	62.2%	68.4%	78.6%	46.8%
TERMINAL (d)	4/11 (36%)	8/10 (80%)	5/9 (56%)	5/9 (56%)	8/11 (73%)	4/8 (50%)
FIRST INCIDENCE	109	192	200	165	184	184
STATISTICAL TESTS						
LIFE TABLE	P=0.344N	P=0.071	P=0.406	P=0.174	P=0.203	P=0.614
POLY 3	P=0.324N	P=0.008 **	P=0.245	P=0.129	P=0.565	
POLY 1.5	P=0.420N	P<0.001 ***	P=0.158	P=0.057	P=0.006 **	P=0.476
POLY 6	P=0.233N	P=0.027 *	P=0.332	P=0.210	P=0.078	P=0.622
LOGISTIC REGRESSION	P=0.416N	P=0.006 **	P=0.204	P=0.053	P=0.051	P=0.533
COCH-ARM / FISHERS	P=0.498	P<0.001 **	P=0.106	P=0.019 *	P=0.002 **	P=0.355

All Organs
Benign Tumors

Dose	All Organs		Males		Females	
	VEHICLE	CONTROL	3125 PPM	6250 PPM	25000 PPM	50000 PPM
TUMOR RATES	#	#	#	#	#	#
OVERALL (a)	7/30 (23%)	12/15 (80%)	7/15 (47%)	9/15 (60%)	11/15 (73%)	5/15 (33%)
POLY-3 RATE (b)	7/16.59	12/14.03	7/11.25	9/13.16	11/14.00	5/10.68
POLY-3 PERCENT (g)	42.2%	85.6%	62.2%	68.4%	78.6%	46.8%
TERMINAL (d)	4/11 (36%)	8/10 (80%)	5/9 (56%)	5/9 (56%)	8/11 (73%)	4/8 (50%)
FIRST INCIDENCE	109	192	200	165	184	184
STATISTICAL TESTS						
LIFE TABLE	P=0.344N	P=0.071	P=0.406	P=0.174	P=0.203	P=0.614
POLY 3	P=0.324N	P=0.008 **	P=0.245	P=0.129	P=0.565	
POLY 1.5	P=0.420N	P<0.001 ***	P=0.158	P=0.057	P=0.006 **	P=0.476
POLY 6	P=0.233N	P=0.027 *	P=0.332	P=0.210	P=0.078	P=0.622
LOGISTIC REGRESSION	P=0.416N	P=0.006 **	P=0.204	P=0.053	P=0.051	P=0.533
COCH-ARM / FISHERS	P=0.498	P<0.001 **	P=0.106	P=0.019 *	P=0.002 **	P=0.355

Date: 07/22/02

Statistical Analysis of Primary Tumors in Mice (TG.AC HETEROZYGOUS TRANSGENIC)
Terminal Sacrifice at 40 weeksEXPERIMENT: 99033 TEST: 01
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

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Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males 12500 PPM	25000 PPM	Females 12500 PPM	25000 PPM
All Organs							
Malignant Tumors							
TUMOR RATES							
# # # # # # # #							
OVERALL (a)							
OVERALL (a)		1/30 (3%)	0/15 (0%)	4/15 (27%)	2/15 (13%)	2/15 (13%)	2/15 (13%)
POLY-3 RATE (b)		1/15.50	0/14.31	4/12.30	2/14.97	2/13.91	2/12.70
POLY-3 PERCENT (g)		6.5%	0.0%	32.5%	13.4%	14.4%	15.7%
TERMINAL (d)		0/9 (0%)	0/12 (0%)	0/8 (0%)	0/12 (0%)	0/11 (0%)	0/10 (0%)
FIRST INCIDENCE		1.97	---	1.38	1.99	1.38	2.00
STATISTICAL TESTS							
LIFE TABLE							
POLY 3		P=0.383	P=0.500N	P=0.104	P=0.526	P=0.452	P=0.464
POLY 1.5		P=0.374	P=0.516N	P=0.088	P=0.487	P=0.460	P=0.426
POLY 6		P=0.346	P=0.557N	P=0.056	P=0.408	P=0.387	P=0.368
POLY 6		P=0.388	P=0.491N	P=0.122	P=0.538	P=0.509	P=0.465
LOGISTIC REGRESSION		P=0.141	P=0.757N	P=0.028 *	P=0.141	P=0.172	P=0.288
COCH-ARM / FISHERS		P=0.252	P=0.667N	P=0.036 *	P=0.254	P=0.254	P=0.254
All Organs							
Malignant Tumors							
TUMOR RATES							
# # # # # # # #							
OVERALL (a)							
OVERALL (a)		1/30 (3%)	1/15 (20%)	1/15 (7%)	2/15 (13%)	0/15 (0%)	2/15 (13%)
POLY-3 RATE (b)		1/15.92	3/13.98	1/10.91	2/11.80	0/13.80	2/10.56
POLY-3 PERCENT (g)		6.3%	21.5%	9.2%	16.9%	0.0%	18.9%
TERMINAL (d)		0/11 (0%)	0/9 (0%)	0/9 (0%)	1/9 (11%)	0/11 (0%)	0/8 (0%)
FIRST INCIDENCE		109	192	148	97	---	215
STATISTICAL TESTS							
LIFE TABLE							
POLY 3		P=0.538	P=0.232	P=0.627	P=0.338	P=0.623N	P=0.351
POLY 1.5		P=0.548N	P=0.245	P=0.682	P=0.389	P=0.529N	P=0.349
POLY 6		P=0.581	P=0.179	P=0.650	P=0.347	P=0.569N	P=0.310
LOGISTIC REGRESSION		P=0.513N	P=0.297	P=0.703	P=0.417	P=0.504N	P=0.382
COCH-ARM / FISHERS		P=0.428	P=0.028 *	P=0.579	P=0.144	P=0.736N	P=0.254
		P=0.471	P=0.101	P=0.561	P=0.254	P=0.667N	P=0.254

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice (TG AC HETEROZOYGOUS TRANSGENIC)

EXPERIMENT: 99033 TEST: 01
Terminal Sacrifice at 40 weeks
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

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Dose	All Organs		Malignant and Benign Tumors		Males		Females	
	VEHICLE	CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM	50000 PPM
TUMOR RATES								
OVERALL (a)			10/30 (33%)	9/15 (60%)	7/15 (47%)	8/15 (53%)	11/15 (73%)	11/15 (73%)
POLY-3 RATE (b)			10/16.58	9/15.00	7/12.30	8/15.00	11/14.04	11/14.14
POLY-3 PERCENT (g)			60.3%	60.0%	56.9%	53.3%	78.3%	77.8%
TERMINAL (d)			5/9 (56%)	6/12 (50%)	3/8 (38%)	5/12 (42%)	8/11 (73%)	7/10 (70%)
FIRST INCIDENCE			76	198	138	199	138	180
STATISTICAL TESTS								
LIFE TABLE			P=0.194	P=0.319N	P=0.498N	P=0.254N	P=0.571	P=0.487
POLY 3			P=0.074	P=0.641N	P=0.588N	P=0.485N	P=0.228	P=0.238
POLY 1.5			P=0.042 *	P=0.387	P=0.541	P=0.553	P=0.069	P=0.077
POLY 6			P=0.095	P=0.459N	P=0.438N	P=0.319N	P=0.427	P=0.429
LOGISTIC REGRESSION			P=0.026 *	P=0.597	P=0.508	P=0.640N	P=0.148	P=0.117
COCH-ARM / FISHERS			P=0.008 **	P=0.083	P=0.292	P=0.166	P=0.013 *	P=0.013 *
Dose								
VEHICLE			3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM	50000 PPM
CONTROL								
TUMOR RATES								
OVERALL (a)			7/30 (23%)	12/15 (80%)	8/15 (53%)	11/15 (73%)	11/15 (73%)	11/15 (73%)
POLY-3 RATE (b)			7/16.59	12/14.03	8/12.10	11/14.12	11/14.00	11/14.26
POLY-3 PERCENT (g)			42.2%	85.6%	66.1%	77.9%	78.6%	62.1%
TERMINAL (d)			4/11 (36%)	8/10 (80%)	5/9 (56%)	6/9 (67%)	8/11 (73%)	4/8 (50%)
FIRST INCIDENCE			109	192	148	97	184	267
STATISTICAL TESTS								
LIFE TABLE			P=0.520	P=0.071	P=0.275	P=0.071	P=0.174	P=0.330
POLY 3			P=0.547	P=0.008 **	P=0.171	P=0.035 *	P=0.032 *	P=0.246
POLY 1.5			P=0.415	P<0.001 **	P=0.087	P=0.008 **	P=0.006 **	P=0.162
POLY 6			P=0.506N	P=0.027 *	P=0.262	P=0.079	P=0.078	P=0.332
LOGISTIC REGRESSION			P=0.371	P=0.006 **	P=0.090	P=0.006 **	P=0.051	P=0.200
COCH-ARM / FISHERS			P=0.234	P<0.001 **	P=0.048 *	P=0.002 **	P=0.002 **	P=0.106

- (a) Number of tumor-bearing animals / number of animals examined at site.
- (b) Number of tumor-bearing animals / Poly-3 number
- (d) Observed incidence at terminal kill
- (f) Beneath the control incidence are the P-values associated with the trend

test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death.

Logistic regression is an alternative method for analyzing the incidence of non-fatal tumors. The Cochran-Armitage and Fishers exact tests compare directly the overall incidence rates

For all tests a negative trend is indicated by N
(e) Value of Statistic cannot be computed.

(G) Poly-3 adjusted lifetime tumor incidence.

(I) Interim sacrifice

(T) Terminal sacrifice

Tumor rates based on number of animals necropsied.

* To the right of any statistical result, indicates significance at ($P \leq 0.05$).
** To the right of any statistical result, indicates significance at ($P \leq 0.01$).

NTP Experiment-Test: 99033-02
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PERIRPT03
Date: 07/22/02
Time: 08:35:00

Facility: BIORELIANCE
Chemical CAS #: 22839-47-0
Lock Date: 07/20/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-02
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:35:00

	MICE: P53+/- (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY							
Animals Initially In Study		15	15	15	15	15	15
Early Deaths		1	1	1			
Moribund Sacrifice							
Natural Death							
Survivors		14	14	14	15	15	15
Terminal Sacrifice							
Animals Examined Microscopically		15	15	15	15	15	15
ALIMENTARY SYSTEM							
Liver							
Infiltration Cellular, Focal, Lymphocyte	(15) 4 (27%)	(15) 3 (20%)	(15) 4 (27%)	(15) 6 (40%)	(15) 4 (27%)	(15) 3 (20%)	(15) 1 (7%)
Necrosis, Focal							
Pigmentation, Focal, Hemosiderin	1 (7%)						
Tension Lipidosis	1 (7%)						
Hepatocyte, Necrosis, Focal							
Hepatocyte, Vacuolization							
Cytoplasmic, Focal							
Salivary Glands							
Infiltration Cellular, Focal, Lymphocyte	(15) 6 (40%)						
CARDIOVASCULAR SYSTEM							
None							
ENDOCRINE SYSTEM							
Adrenal Cortex							
Hyperplasia, Focal	(15)	(15)	(14)	(15)	(15)	(15)	
Subcapsular, Hyperplasia, Focal	12 (80%)	13 (87%)	13 (93%)	15 (100%)	15 (100%)	15 (100%)	
Pituitary Gland							
Pars Intermedia, Hypertrophy	(9)	(14)	(13)	(14)	(11)	(14)	
Thyroid Gland							
Ectopic Thymus	(14) 2 (14%)	(13) 1 (8%)	(14) 1 (7%)	(14) 3 (21%)	2 (18%) 1 (8%)	2 (14%) 1 (5%)	
GENERAL BODY SYSTEM							
None							

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-02
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:35:00

	VEHICLE	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
GENITAL SYSTEM						
Ovary	(15)	(15)	(14) 1 (7%)	(15)	(15)	(15)
Atrophy						
Uterus	(15)	(15) 1 (7%)	(15)	(15)	(15)	(15)
Hydrometra						
Endometrium						
Hyperplasia, Cystic	14 (93%)	14 (93%)	15 (100%)	14 (93%)	15 (100%)	15 (100%)
HEMATOPOIETIC SYSTEM						
Lymph Node, Mandibular	(15)	(13)	(13)	(15)	(15) 1 (7%)	(14)
Congestion						
Hyperplasia	1 (7%)	2 (15%)	1 (7%)	1 (7%)	1 (7%)	
Hyperplasia, Histiocytic	1 (7%)					
Lymph Node, Mesenteric	(15)	(14)	(14)	(14)	(15)	(15)
Hyperplasia						
Spleen	(15)	(15) 1 (7%)	(15)	(15)	(15)	(15)
Depletion						
Cellular, Diffuse						
Hematopoietic Cell Proliferation	3 (20%)	4 (27%)	1 (7%)	3 (20%)	1 (7%)	1 (7%)
Pigmentation						
Thymus	(14) 1 (7%)	(14)	(14)	(15)	(15) 1 (7%)	(15)
Atrophy, Focal						
Hyperplasia						
Hyperplasia, Atypical, Focal			1 (7%)	1 (7%)	1 (7%)	
INTEGMENTARY SYSTEM						
None						
MUSCULOSKELETAL SYSTEM						
Bone	(15)	(1)				
Femur, Fibrous Osteodystrophy, Focal						
NERVOUS SYSTEM						
Brain	(15)	(14)	(14)	(15) 1 (7%)	(15)	(15)
Medulla, Cyst Epithelial Inclusion						

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-02
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PEIIRPPT03
Date: 07/22/02
Time: 08:35:00

MICE: P53+/- (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
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RESPIRATORY SYSTEM

Lung	(15)	(14)	(15)	(15)	(15)	(15)
Infiltration Cellular, Focal, Lymphocyte						

SPECIAL SENSES SYSTEM

Harderian Gland	(15)					
Inflammation, Chronic Active						

URINARY SYSTEM

Kidney	(15)	(14)	(15)	(15)	(15)	
Infiltration Cellular, Focal, Lymphocyte		1 (7%)		1 (7%)		
Glomerulus, Hyalinization						
Renal Tubule, Dilatation, Diffuse	1 (7%)	2 (14%)	3 (20%)			
Renal Tubule, Dilatation, Focal	4 (27%)	5 (36%)	2 (13%)	5 (33%)	4 (27%)	4 (27%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-02
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:35:00

	MICE: P53+/- (C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY							
Animals Initially In Study							
Early Deaths		15	15	15	15	15	15
Natural Death		1		1		1	
Moribund Sacrifice				1			
Survivors		14	15	13	15	14	14
Terminal Sacrifice					14	14	
Animals Examined Microscopically		15	15	15	15	15	15
ALIMENTARY SYSTEM							
Liver		(14)	(15)	(15)	(14)	(15)	(15)
Infiltration Cellular, Focal, Lymphocyte		3 (21%)	2 (13%)	4 (27%)	2 (14%)	4 (27%)	
Inflammation, Chronic		1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	
Necrosis, Focal		1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	
Salivary Glands		(14)	(1)	(1)	(1)	(1)	
Infiltration Cellular, Focal, Lymphocyte		9 (64%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	
Tooth							
Peridental Tissue, Cyst							
CARDIOVASCULAR SYSTEM							
None							
ENDOCRINE SYSTEM							
Adrenal Cortex		(14) 14 (100%)	(15) 14 (93%)	(15) 12 (80%)	(15) 10 (67%)	(15) 13 (87%)	
Atrophy			1	2 (20%)	1 (7%)	3 (20%)	
Hypertrrophy, Focal		1 (7%)	2 (13%)	2 (13%)	2 (13%)	1 (7%)	
Subcapsular							
Hyperplasia, Focal							
GENERAL BODY SYSTEM							
None							
GENITAL SYSTEM							
a Number of animals examined microscopically at site and number of animals with lesion							

NTP Experiment-Test: 99033-02
Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PEIRPT03
Date: 07/22/02
Time: 08:35:00

	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
GENITAL SYSTEM - CONT						
Epididymis	(15)	(15)	(15)	(15)	(14)	(15)
Epididymis, Degeneration, Focal	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Testes	(15)	(15)	(15)	(15)	(14)	(15)
Mineralization, Focal	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Germinal Epithelium, Degeneration, Diffuse	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Germinal Epithelium, Degeneration, Focal	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Rete Testes, Inflammation, Focal	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
HEMATOPOIETIC SYSTEM						
Bone Marrow	(14)	(14)	(14)	(14)	(15)	(15)
Hyperplasia	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Lymph Node	(1)	(1)	(1)	(1)	(1)	(1)
Iliac, Pigmentation, Focal	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Lymph Node, Mandibular	(14)	(15)	(14)	(14)	(15)	(15)
Hyperplasia	3 (20%)	2 (13%)	2 (13%)	2 (13%)	1 (7%)	1 (7%)
Lymph Node, Mesenteric	(14)	(14)	(15)	(13)	(14)	(15)
Hyperplasia	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Lymph Node, Mediastinal	(13)	(14)	(14)	(13)	(12)	(13)
Hyperplasia	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Spleen	(14)	(15)	(15)	(15)	(14)	(15)
Hematopoietic Cell Proliferation	1 (8%)	1 (8%)	1 (8%)	1 (8%)	2 (13%)	2 (13%)
Hyperplasia, Lymphoid	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Thymus	(14)	(15)	(15)	(14)	(15)	(14)
Atrophy, Diffuse	1 (7%)	1 (7%)	1 (7%)	2 (14%)	2 (14%)	2 (14%)
Atrophy, Focal	1 (7%)	1 (7%)	1 (7%)	2 (14%)	2 (14%)	2 (14%)
INTEGUMENTARY SYSTEM						
None						
MUSCULOSKELETAL SYSTEM						
None						
NERVOUS SYSTEM						
Brain	(14)	(15)	(15)	(15)	(14)	(15)
Hydrocephalus	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)	1 (7%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-02
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Report: PETIRPT03
 Date: 07/22/02
 Time: 08:35:00

	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
MICE: P53 +/- (C57BL/6) MALE						
NERVOUS SYSTEM - CONT						
Corpus Callosum, Medulla, Vacuolization				1 (7%)		1 (7%)
Cytoplasmic, Focal						
Medulla, Vacuolization				(1)		
Cytoplasmic, Focal						
Ventricle, Hydrocephalus						
Peripheral Nerve				(1)		
Vacuolization				(1)		
Cytoplasmic, Diffuse						
Spinal Cord				(1)		
Gliosis						
Vacuolization				1 (100%)		
Cytoplasmic, Focal				1 (100%)		
RESPIRATORY SYSTEM						
Lung						
Infiltration						
Cellular, Focal, Lymphocyte				(15)		
Inflammation, Chronic Active, Diffuse						
Perivasculat						
Infiltration						
Cellular,						
Lymphocyte						
Nose						
Inflammation, Acute				(14)		
SPECIAL SENSES SYSTEM						
Eye						
Developmental Malformation						
Harderian Gland						
Infiltration						
Cellular, Focal, Lymphocyte				(14)		
Inflammation, Chronic Active						
URINARY SYSTEM						
Kidney						
Infiltration						
Cellular, Focal, Lymphocyte						
Nephropathy						
Renal Tubule, Dilatation, Diffuse						
Renal Tubule, Dilatation, Focal						

- a Number of animals examined microscopically at site and number of animals with lesion

END OF REPORT

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS TRANSGENIC MODEL EVALUATION II (ASPARTAME)
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:35:18

Facility: BIORELIANCE
Chemical CAS #: 22839-47-0
Lock Date: 07/20/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-02 Study Type: 26-39 WEEKS
Route: DOSED FEED

INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT05
Date: 07/22/02
Time: 08:35:18

MICE: P53+ / - (C57BL/6)	FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
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DISPOSITION SUMMARY

Animals Initially in Study	15	15	15	15	15	15	15
Early Deaths							
Moribund Sacrifice	1	1	1				
Natural Death							
Survivors							
Terminal Sacrifice	14	14	14	14	15	15	15
Examined Microscopically	15	15	15	15	15	15	15

ALIMENTARY SYSTEM

Gallbladder	(14)						
Intestine Large, Cecum	(15)						
Liver	(15)						
Sarcoma	(15)						

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

Pituitary Gland	(9)	(14)	(13)	(14)	(11)	(14)	
Pars Distalis, Adenoma	1 (11%)						
Thyroid Gland	(14)	(13)	(14)	(14)	(13)	(15)	
Follicular Cell, Adenoma					1 (8%)		

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

None

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:35:18
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P53+ / - (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
HEMATOPOIETIC SYSTEM						
Lymph Node	(15)	(13)	(13)	(14)	(14)	(1)
Lymph Node, Mandibular	(15)	(14)	(14)	(14)	(14)	(15)
Lymph Node, Mesenteric				1 (78)	1 (78)	(15)
Sarcoma	(12)	(13)	(13)	(12)	(12)	(13)
Lymph Node, Mediastinal	(15)	(15)	(15)	(15)	(15)	(15)
Spleen	(14)	(14)	(14)	(15)	(15)	(15)
Thymus				1 (15)	1 (15)	(15)
INTEGUMENTARY SYSTEM						
Mammary Gland	(13)	(14)	(14)	(15)	(12)	(14)
Carcinoma	1 (8%)		(1)	1 (78)		(15)
Skin	(15)		1 (100%)			
Subcutaneous Tissue, Fibrosarcoma						
MUSCULOSKELETAL SYSTEM						
Bone	(15)		(1)			(15)
Femur, Osteosarcoma	1 (78%)		1 (100%)			1 (78)
Vertebra, Osteosarcoma						
NERVOUS SYSTEM						
None						
RESPIRATORY SYSTEM						
Lung	(15)	(15)	(14)	(15)	(15)	(15)
SPECIAL SENSES SYSTEM						
None						

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS TRANSGENIC MODEL EVALUATION II (ASPARTAME)
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:35:18

MICE: P53+ / - (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
URINARY SYSTEM						
Kidney	(15)	(14)	(15)	(15)	(15)	(15)
SYSTEMIC LESIONS						
Multiple Organs	* (15) 1 (7%)	* (15)	* (15)	* (15)	* (15) 1 (7%)	* (15)
Lymphoma Malignant						

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED
 MICE : P53+/- (C57BL/6) FEMALE

	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
MICE : P53+/- (C57BL/6) FEMALE						

TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	4	2	2	1	1
Total Primary Neoplasms	4	2	3	2	1
Total Animals with Benign Neoplasms	1				1
Total Benign Neoplasms	1			1	1
Total Animals with Malignant Neoplasms	3				1
Total Malignant Neoplasms	3	2	2	1	1
Total Animals with Metastatic Neoplasms					
Total Metastatic Neoplasm					
Total Animals with Malignant Neoplasms					
Uncertain Primary Site					
Total Animals with Neoplasms Uncertain-					
Benign or Malignant					
Total Uncertain Neoplasms					

a Number of animals examined microscopically at site and number of animals with lesion

b Primary tumors: all tumors except metastatic tumors

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:35:18
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P53+/- (C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY						
Animals Initially in Study	15	15	15	15	15	15
Early Deaths	1		1		1	
Natural Death			1			1
Moribund Sacrifice						
Survivors	14	15	13	15	14	14
Terminal Sacrifice						
Animals Examined Microscopically	15	15	15	15	15	15
ALIMENTARY SYSTEM						
Intestine Small, Duodenum	(14)					
Poly Adenomatous						
Liver	(14)	(15)				
Salivary Glands	(14)	(1)	(15)			
CARDIOVASCULAR SYSTEM						
None						
ENDOCRINE SYSTEM						
None						
GENERAL BODY SYSTEM						
None						
GENITAL SYSTEM						
Prostate	(14)	(15)	(15)	(15)	(14)	(15)
Sarcoma					1 (7%)	

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:35:18
TRANSGENIC MODEL EVALUATION II (ASPARTAME) (a)

	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
HEMATOPOIETIC SYSTEM						
Lymph Node, Mandibular	(14)	(15)	(14)	(15)	(14)	(15)
Lymph Node, Mesenteric	(14)	(14)	(15)	(13)	(14)	(15)
Lymph Node, Mediastinal	(13)	(14)	(14)	(13)	(12)	(13)
Spleen	(14)	(15)	(15)	(15)	(14)	(15)
Thymus	(14)	(15)	(14)	(14)	(14)	(14)
INTEGUMENTARY SYSTEM						
Skin	(15)					
Subcutaneous Tissue, Sarcoma		(15)				
MUSCULOSKELETAL SYSTEM						
NERVOUS SYSTEM						
None						
RESPIRATORY SYSTEM						
Lung	(15)	(15)	(15)	(15)	(14)	(15)
SPECIAL SENSES SYSTEM						
None						
URINARY SYSTEM						
Kidney	(14)	(15)	(15)	(15)	(14)	(15)

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: 26-39 WEEKS Date: 07/22/02
Route: DOSED FEED Time: 08:35:18

Report: PEIRPT05
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

	MICE: P53+/- (C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
SYSTEMIC LESIONS							
Multiple Organs	* (15)	* (15)	* (15)	* (15)	* (15)	* (15)	* (15)
Lymphoma Malignant		2 (13%)					

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-02 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: 26-39 WEEKS
 Route: DOSED FEED

MICE: p53 +/- (C57BL/6)	MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
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TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)

Total Primary Neoplasms

Total Animals with Benign Neoplasms

Total Benign Neoplasms

Total Animals with Malignant Neoplasms

Total Malignant Neoplasms

Total Animals with Metastatic Neoplasms

Total Metastatic Neoplasm

Total Animals with Malignant Neoplasms

Uncertain Primary Site

Total Animals with Neoplasms Uncertain-

Benign or Malignant

Total Uncertain Neoplasms

a Number of animals examined microscopically at site and number of animals with lesion

b Primary tumors: all tumors except metastatic tumors

Report: PEIRPT05
 Date: 07/22/02
 Time: 08:35:18

END OF REPORT

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 02
TEST TYPE: 26-39 WEEKS
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDA

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:36:04
PAGE: 1
NTP C#: C99033
CAS: 22839-47-0

REASONS FOR REMOVAL: ALL

REMOVAL DATE RANGE: ALL
TREATMENT GROUPS: INCLUDE ALL

NTP
LAB: BIOPRELIANCE
EXPERIMENT: 99033 TEST: 02
TEST TYPE: 26-39 WEEKS
CONT: NO1-ES-65406
PATHOLOGIST: LANNING, LYnda
Mice(P53 Heterozygous Transgenic)

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENETIC MODEL EVALUATION II(ASPARTAME)

REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:36:04
NTP C#: C99033
CAS: 22839-47-0

FOR ALL DOSES THE TUMOR RATES IN THE FOLLOWING TISSUES/ORGANS ARE
BASED ON NUMBER OF TISSUES EXAMINED. IN OTHER TISSUES/ORGANS RATES
ARE BASED ON THE NUMBER OF ANIMALS NECROPSIED.

Liver
Pituitary Gland
Prostate
Thyroid Gland

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 02
TEST TYPE: 26-39 WEEKS
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDA

ROUTE: DOSED FEED

REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:36:04
NTP C#: C99033
CAS: 22839-47-0

SUMMARY OF STATISTICALLY SIGNIFICANT ($P \leq .05$) RESULTS
IN THE ANALYSIS OF TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Female Mice

Organ Morphology

All Organs Malignant and Benign Tumors

Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males 12500 PPM	25000 PPM	50000 PPM
All Organs						
Malignant Lymphoma: Histiocytic, Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type						
TUMOR RATES						
OVERALL (a)	#	#	#	#	#	#
POLY-3 RATE (b)	0/15 (0%)	0/15 (0%)	2/15 (13%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
POLY-3 PERCENT (g)	0/14.05	0/15.00	2/15.00	0/15.00	0/14.01	0/14.02
TERMINAL (d)	0.0%	0.0%	13.3%	0.0%	0.0%	0.0%
FIRST INCIDENCE	0/14 (0%)	0/15 (0%)	0/13 (0%)	0/15 (0%)	0/14 (0%)	0/14 (0%)
STATISTICAL TESTS						
LIFE TABLE	#	#	#	#	#	#
POLY 3	P=0.389N (e)	P=0.378N (e)	P=0.379N (e)	P=0.247 (e)	P=0.247 (e)	P=0.15 (0%) (e)
POLY 1.5	P=0.379N (e)	P=0.379N (e)	P=0.244 (e)	P=0.244 (e)	P=0.14.01 (e)	0/14.02 (e)
POLY 6	P=0.377N (e)	P=0.236N (e)	P=0.175 (e)	P=0.175 (e)	P=0.14 (0%) (e)	0/14 (0%) (e)
LOGISTIC REGRESSION						
COCH-ARM / FISHERS	P=0.381N (e)	P=0.381N (e)	P=0.241 (e)	P=0.241 (e)	P=0.241 (e)	P=0.241 (e)
Dose						
Dose						
All Organs						
Malignant Lymphoma: Histiocytic, Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type						
TUMOR RATES						
OVERALL (a)	#	#	#	#	#	#
POLY-3 RATE (b)	1/15 (7%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	0/15 (0%)	0/15 (0%)
POLY-3 PERCENT (g)	1/14.00	0/14.05	0/14.23	0/15.00	1/15.00	0/15.00
TERMINAL (d)	7.1%	0.0%	0.0%	6.7%	0.0%	0.0%
FIRST INCIDENCE	1/14 (7%)	0/14 (0%)	0/14 (0%)	1/15 (7%)	0/15 (0%)	0/15 (0%)
STATISTICAL TESTS	#	#	#	#	#	#
LIFE TABLE	P=0.570N (e)	P=0.500N (e)	P=0.486N (T)	P=0.486N (T)	P=0.486N (T)	P=0.486N (T)
POLY 3	P=0.578N (e)	P=0.499N (e)	P=0.497N (T)	P=0.497N (T)	P=0.486N (T)	P=0.486N (T)
POLY 1.5	P=0.581N (e)	P=0.498N (e)	P=0.494N (e)	P=0.494N (e)	P=0.487N (e)	P=0.487N (e)
POLY 6	P=0.576N (e)	P=0.500N (e)	P=0.499N (e)	P=0.499N (e)	P=0.486N (e)	P=0.486N (e)
LOGISTIC REGRESSION						
COCH-ARM / FISHERS	P=0.586N (e)	P=0.500N (e)	P=0.500N (e)	P=0.500N (e)	P=0.500N (e)	P=0.500N (e)

Date: 07/22/02
Statistical Analysis of Primary Tumors in Mice(P53 Heterozygous Transgenic)

EXPERIMENT: 99033 TEST: 02
TRANSGENIC MODEL EVALUATION II (ASPARTAME)
Terminal Sacrifice at 40 weeks

Page 2

		Males			Females		
Dose		VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
All Organs							
Malignant Tumors							
TUMOR RATES	#	#	#	#	#	#	#
OVERALL (a)	0/15 (0%)	0/15 (0%)	2/15 (13%)	0/15 (0%)	1/15 (7%)	1/15 (7%)	1/15 (0%)
POLY-3 RATE (b)	0/14.05	0/15.00	2/15.00	0/15.00	1/14.01	1/15.00	1/15.00
POLY-3 PERCENT (g)	0.0%	0.0%	13.3%	0.0%	7.1%	6.7%	6.7%
TERMINAL (d)	0/14 (0%)	0/15 (0%)	0/15 (0%)	1/14 (7%)	0/14 (0%)	0/14 (0%)	0/14 (0%)
FIRST INCIDENCE	---	---	274 (T)	---	71	---	---
STATISTICAL TESTS							
LIFE TABLE	P=0.373 (e)	P=0.394 (e)	P=0.391 (e)	P=0.395 (e)	P=0.562 (e)	P=0.247 (e)	P=0.500 (e)
POLY 3	P=0.391 (e)	P=0.244 (e)	P=0.244 (e)	P=0.248 (e)	P=0.175 (e)	P=0.499 (e)	P=0.513 (e)
POLY 1.5	P=0.391 (e)	P=0.244 (e)	P=0.244 (e)	P=0.248 (e)	P=0.500 (e)	P=0.498 (e)	P=0.511 (e)
POLY 6	P=0.395 (e)	P=0.248 (e)	P=0.248 (e)	P=0.248 (e)	P=0.500 (e)	P=0.514 (e)	P=0.514 (e)
POLY-3 PERCENT (g)	0.0%	0.0%	13.3%	0.0%	7.1%	6.7%	6.7%
LOGISTIC REGRESSION	---	---	---	---	---	---	---
COCH-ARM / FISHERS	P=0.373 (e)	P=0.562 (e)	P=0.373 (e)	P=0.562 (e)	P=0.373 (e)	P=0.500 (e)	P=0.500 (e)
All Organs							
Malignant Tumors							
Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM	
TUMOR RATES	#	#	#	#	#	#	#
OVERALL (a)	3/15 (20%)	0/15 (0%)	2/15 (13%)	2/15 (13%)	1/15 (7%)	1/15 (7%)	1/15 (0%)
POLY-3 RATE (b)	3/14.00	0/14.05	2/14.23	2/15.00	1/15.00	1/15.00	1/15.00
POLY-3 PERCENT (g)	21.4%	0.0%	14.1%	13.3%	6.7%	6.7%	6.7%
TERMINAL (d)	3/14 (21%)	0/14 (0%)	2/14 (14%)	2/15 (13%)	1/15 (7%)	1/15 (7%)	1/15 (7%)
FIRST INCIDENCE	275 (T)						
STATISTICAL TESTS							
LIFE TABLE	P=0.311N (P=0.311N)	P=0.115N (P=0.105N)	P=0.500N (P=0.492N)	P=0.467N (P=0.467N)	P=0.273N (P=0.273N)	P=0.273N (P=0.274N)	P=0.273N (P=0.273N)
POLY 3	P=0.320N (P=0.320N)	P=0.103N (P=0.105N)	P=0.486N (P=0.498N)	P=0.469N (P=0.467N)	P=0.274N (P=0.273N)	P=0.274N (P=0.273N)	P=0.274N (P=0.273N)
POLY 1.5	P=0.313N (P=0.311N)	P=0.105N (P=0.112N)	P=0.498N (P=0.500N)	P=0.467N (P=0.500N)	P=0.273N (P=0.299N)	P=0.273N (P=0.299N)	P=0.273N (P=0.299N)
POLY 6	P=0.313N (P=0.339N)	P=0.112N (P=0.500N)	P=0.500N (P=0.500N)	P=0.466N (P=0.500N)	P=0.273N (P=0.299N)	P=0.273N (P=0.299N)	P=0.273N (P=0.299N)
LOGISTIC REGRESSION	---	---	---	---	---	---	---
COCH-ARM / FISHERS	P=0.339N (P=0.339N)	P=0.500N (P=0.500N)	P=0.500N (P=0.500N)	P=0.466N (P=0.500N)	P=0.273N (P=0.299N)	P=0.273N (P=0.299N)	P=0.273N (P=0.299N)

Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males 12500 PPM	25000 PPM	50000 PPM
All Organs						
Malignant and Benign Tumors						
TUMOR RATES						
OVERALL (a)	#	#	#	#	#	#
POLY-3 RATE (b)	0/15 (0%)	0/15 (0%)	2/15 (13%)	0/15 (0%)	1/15 (7%)	2/15 (13%)
POLY-3 PERCENT (g)	0/14. 05	0/15. 00	2/15. 00	0/15. 00	1/14. 01	2/15. 00
TERMINAL (d)	0.0%	0.0%	7.1%	0.0%	13.3%	13.3%
FIRST INCIDENCE	0/14 (0%)	0/15 (0%)	1/14 (7%)	1/14 (7%)	1/14 (7%)	1/14 (7%)
STATISTICAL TESTS						
LIFE TABLE	#	#	#	#	#	#
POLY 3	P=0.119	(e)	P=0.247	(e)	P=0.500	P=0.240
POLY 1.5	P=0.123	(e)	P=0.247	(e)	P=0.499	P=0.247
POLY 6	P=0.122	(e)	P=0.244	(e)	P=0.498	P=0.244
LOGISTIC REGRESSION	P=0.123	(e)	P=0.248	(e)	P=0.500	P=0.248
COCH-ARM / FISHERS	P=0.184	(e)	P=0.175	(e)	P=0.500	P=0.233
	P=0.118	(e)	P=0.241	(e)	P=0.500	P=0.241
All Organs						
Malignant and Benign Tumors						
Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Females 12500 PPM	25000 PPM	50000 PPM
All Organs						
Malignant and Benign Tumors						
TUMOR RATES						
OVERALL (a)	#	#	#	#	#	#
POLY-3 RATE (b)	4/15 (27%)	0/15 (0%)	2/15 (13%)	2/15 (13%)	1/15 (7%)	1/15 (7%)
POLY-3 PERCENT (g)	4/14. 00	0/14. 05	2/14. 23	2/15. 00	1/15. 00	1/15. 00
TERMINAL (d)	28.6%	0.0%	14.1%	13.3%	6.7%	6.7%
FIRST INCIDENCE	4/14 (29%)	0/14 (0%)	2/14 (14%)	2/15 (13%)	1/15 (7%)	1/15 (7%)
STATISTICAL TESTS	#	#	#	#	#	#
LIFE TABLE	P=0.214N	P=0.056N	P=0.326N	P=0.293N	P=0.147N	P=0.147N
POLY 3	P=0.217N	P=0.044N*	P=0.318N	P=0.293N	P=0.141N	P=0.141N
POLY 1.5	P=0.221N	P=0.043N*	P=0.311N	P=0.295N	P=0.142N	P=0.142N
POLY 6	P=0.215N	P=0.044N*	P=0.324N	P=0.293N	P=0.141N	P=0.141N
LOGISTIC REGRESSION	P=0.214N	(e)	P=0.326N	P=0.293N	P=0.143N	P=0.143N
COCH-ARM / FISHERS	P=0.238N	P=0.050N	P=0.326N	P=0.326N	P=0.165N	P=0.165N

(a) Number of tumor-bearing animals / number of animals examined at site.

(b) Number of tumor-bearing animals / Poly-3 number

(d) Observed incidence at terminal kill.

(f) Beneath the control incidence are the P-values associated with the trend

test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. Logistic regression is an alternative method for analyzing the incidence of non-fatal tumors. The Cochran-Armitage and Fishers exact tests compare directly the overall incidence rates. For all tests a negative trend is indicated by N.

(e) Value of Statistic cannot be computed.

(g) Poly-3 adjusted lifetime tumor incidence.

(I) Interim sacrifice

(T) Terminal sacrifice

Tumor rates based on number of animals necropsied.

* To the right of any statistical result, indicates significance at ($P \leq 0.05$).

** To the right of any statistical result, indicates significance at ($P \leq 0.01$).

NTP Experiment-Test: 99033-03
Study Type: SPECIAL STUDY
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
Date: 07/22/02
Time: 08:36:30

Facility: BIORELIANCE
Chemical CAS #: 22839-47-0
Lock Date: 07/20/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-03
 Study Type: SPECIAL STUDY
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIIRPT03
 Date: 07/22/02
 Time: 08:36:30

	MICE: P16 (INK4A) / (+/-)	(C57BL/6)	FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY									
Animals Initially In Study	15		15		15		15		15
Natural Death	2				2				1
Moribund Sacrifice									
Survivors	13		15		13		15		14
Terminal Sacrifice									
Animals Examined Microscopically	15		15		15		15		15
ALIMENTARY SYSTEM									
Liver		(15)		(15)		(15)		(15)	
Hematopoietic Cell Proliferation		1	(7%)						(15)
Infiltration Cellular, Lymphocyte									2 (13%)
Necrosis, Focal									
Hepatocyte, Necrosis, Focal					1	(7%)		1 (7%)	2 (13%)
Salivary Glands		(13)							
Infiltration Cellular, Focal, Lymphocyte		3	(23%)						
CARDIOVASCULAR SYSTEM									
Heart		(15)		(15)		(15)		(15)	
Myocardium, Necrosis, Focal					1	(7%)			
ENDOCRINE SYSTEM									
Adrenal Cortex		(14)		(15)		(13)		(15)	
Accessory Adrenal Cortical Nodule		14	(100%)	15	(100%)	12	(92%)	15 (100%)	1 (7%)
Subcapsular, Hyperplasia, Focal		(14)	(15)		(15)		(15)		15 (100%)
Thyroid Gland									
Ectopic Thymus								2	(13%)
GENERAL BODY SYSTEM									
Tissue NOS									
Abdominal, Fat, Hemorrhage, Focal									

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-03
 Study Type: SPECIAL STUDY
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P16 (INK4A) / (+/-)	(C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM

GENITAL SYSTEM

Ovary	(14)	(15)	(15)	(15)	(15)	(15)
Cyst						
Thecal Cell, Hyperplasia						
Uterus	(14)	(15)	1 (7%)	1 (7%)	1 (7%)	1 (7%)
/ Endometrium, Hyperplasia, Cystic	13 (93%)	13 (87%)	13 (87%)	13 (87%)	13 (87%)	13 (87%)

HEMATOPOIETIC SYSTEM

Lymph Node, Mandibular	(14)	(15)	(13)	(15)	(15)	(15)
Inflammation, Chronic Active	1 (7%)					
Lymph Node, Mesenteric	(14)	(15)	(14)	(15)	(15)	(15)
Hyperplasia, Histiocytic						
Spleen	(14)	(15)	(14)	(15)	(15)	(15)
Accessory Spleen						
Hematopoietic Cell Proliferation	5 (36%)	2 (13%)	4 (29%)	3 (20%)	2 (13%)	3 (20%)
Pigmentation	1 (7%)					
Thymus	(14)	(15)	(14)	(14)	(15)	(15)
Atrophy, Focal		1 (7%)	1 (7%)			

INTEGUMENTARY SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

Spinal Cord	(1)
Vacuolization Cytoplasmic	1 (100%)

RESPIRATORY SYSTEM

Lung	(14)	(14)	(15)	(15)
Alveolar Epithelium, Hyperplasia, Focal	1 (7%)			

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-03
Study Type: SPECIAL STUDY
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P16 (INK4A) / (+/-) (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
None						

SPECIAL SENSES SYSTEM

None

URINARY SYSTEM

Kidney	(13)	(15)	(13)	(15)	(15)	(15)
Nephropathy						
Glomerulus, Hyalinization						
Renal Tubule, Dilatation, Diffuse		1 (7%)				
Renal Tubule, Dilatation, Focal	8 (62%)	7 (47%)	5 (38%)	5 (33%)	1 (7%)	1 (7%)
					5 (33%)	8 (53%)

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-03
 Study Type: SPECIAL STUDY
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:36:30

MICE: P16 (INK4A) / (+/-) (C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY						
Animals Initially In Study	15	15	15	15	15	15
Early Deaths	1	1	1	1	1	1
Survivors	14	14	15	14	14	15
Terminal Sacrifice						
Animals Examined Microscopically	15	15	15	15	15	15

ALIMENTARY SYSTEM

Liver	(15)	(15)	(15)	(14)	(15)	(15)
Infiltration Cellular, Focal, Lymphocyte	2 (13%)					
Necrosis, Focal	2 (13%)					
Hepatocyte, Necrosis, Focal	1 (7%)					
Hepatocyte, Vacuolization Cytoplasmic, Diffuse		1 (7%)	3 (20%)		1 (7%)	4 (27%)
Hepatocyte, Periportal, Vacuolization Cytoplasmic			1 (7%)		1 (7%)	1 (7%)
Hepatocyte, Centrilobular, Vacuolization Cytoplasmic	6 (40%)	11 (73%)	14 (93%)	8 (57%)	13 (87%)	14 (93%)
Salivary Glands	1 (7%)					
Infiltration Cellular, Focal, Lymphocyte	(15)					
	8 (53%)					

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

Adrenal Cortex	(15)	(15)	(15)	(14)	(15)	(15)
Accessory Adrenal Cortical Nodule Subcapsular, Hyperplasia, Focal		1 (7%)		1 (7%)	1 (7%)	1 (7%)

GENERAL BODY SYSTEM

None

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-03
 Study Type: SPECIAL STUDY
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 TRANSGENIC MODEL EVALUATION II (ASPARTAME)

Report: PEIRPT03
 Date: 07/22/02
 Time: 08:36:30

	MICE: P16 (INK4A) / (+/-)	(C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
GENITAL SYSTEM								
Epididymis								
Inflammation, Chronic Active, Focal		(15)	(15)	(15)	(15)	(15)	(15)	(15)
Testes		(15)	(15)	(15)	(15)	(14)	(14)	(14)
Germinal Epithelium, Degeneration			1 (7%)	1 (7%)				
HEMATOPOTETIC SYSTEM								
Lymph Node, Mandibular		(15)	(15)	(15)	(14)	(14)	(14)	(15)
Hyperplasia		1 (7%)	(15)	(15)	1 (7%)	(14)	(14)	(15)
Lymph Node, Mesenteric		(15)	(15)	(15)	2 (13%)	(14)	(14)	(15)
Hyperplasia				(15)	(15)	(14)	(15)	(15)
Spleen		(15)	(15)	(15)				
Atrophy, Diffuse		1 (7%)						
Hematopoietic Cell Proliferation			1 (7%)	2 (13%)	3 (21%)	1 (7%)	1 (7%)	1 (7%)
Pigmentation								
Thymus		(15)	(14)	(15)	(13)	(15)	1 (7%)	1 (7%)
Atrophy, Diffuse		1 (7%)		1 (7%)				
Atrophy, Focal		1 (7%)	2 (14%)			1 (7%)		
INTEGUMENTARY SYSTEM								
None								
MUSCULOSKELETAL SYSTEM								
None								
NERVOUS SYSTEM								
Brain		(15)	(15)	(15)	(14)	(15)	(15)	(15)
Cerebellum, Medulla, Vacuolization				1 (7%)				
Cytoplasmic								
RESPIRATORY SYSTEM								
Lung		(15)	(15)	(15)	(15)	(15)	(15)	(15)
Infiltration Cellular, Focal, Lymphocyte			1 (7%)					

a Number of animals examined microscopically at site and number of animals with lesion

NTPR Experiment-Test: 99033-03
Study Type: SPECIAL STUDY
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P16 (INK4A) / (+/-)	(C57BL/6)	MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
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SPECIAL SENSES SYSTEM

None

URINARY SYSTEM
Kidney
Nephropathy

(15) (15)
1 (78) (15) (15)
3 (20%) (14) (15)

a Number of animals examined microscopically at site and number of animals with lesion

Report: PEIRPT03
Date: 07/22/02
Time: 08:36:30

END OF REPORT

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: SPECIAL STUDY
Route: DOSED FEED

Report: PERIRPT05
Date: 07/22/02
Time: 08:37:41

Facility: BIORELIANCE
Chemical CAS #: 22839-47-0
Lock Date: 07/20/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: SPECIAL STUDY Report: PEIRPT05
Route: DOSED FEED Date: 07/22/02
 Time: 08:37:41

TRANSGENIC MODEL EVALUATION II(ASPARTAME)

MICE: P16 (INK4A) / (+/-) (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY						
Animals Initially in Study	15	15	15	15	15	15
Early Deaths	2		2			
Natural Death						
Moribund Sacrifice						
Survivors	13	15	13	15	15	1
Terminal Sacrifice						
Animals Examined Microscopically	15	15	15	15	15	14
Microscopic						
Macroscopic						
ALIMENTARY SYSTEM						
Gallbladder	(12)	(1)				(14)
Histiocytic Sarcoma		1	(100%)			
Intestine Large, Cecum	(14)					
Leiomyoma						
Liver	(15)	(15)				
Histiocytic Sarcoma		1	(100%)			
Pancreas	2 (13%)					
Histiocytic Sarcoma	(14)	1	(7%)			
		1	(100%)			
CARDIOVASCULAR SYSTEM						
Heart	(15)	(15)				
Hemangiosarcoma						
ENDOCRINE SYSTEM						
Pituitary Gland	(10)	(13)				
Adenoma		1 (8%)				
GENERAL BODY SYSTEM						
None						

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED)
Study Type: SPECIAL STUDY
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:37:41
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P16 (INK4A) / (+/-)	(C57BL/6)	FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
GENITAL SYSTEM								
Ovary								
Histiocytic Sarcoma								
Uterus								
Histiocytic Sarcoma								
HEMATOPOIETIC SYSTEM								
Bone Marrow								
Histiocytic Sarcoma								
Lymph Node, Mandibular								
Histiocytic Sarcoma								
Lymph Node, Mesenteric								
Histiocytic Sarcoma								
Lymph Node, Mediastinal								
Histiocytic Sarcoma								
Spleen								
Hemangiosarcoma								
Histiocytic Sarcoma								
Thymus								
Histiocytic Sarcoma								
INTEGUMENTARY SYSTEM								
Mammary Gland								
Hemangiosarcoma								
MUSCULOSKELETAL SYSTEM								
None								
NERVOUS SYSTEM								
Brain								
Meninges, Histiocytic Sarcoma								

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: SPECIAL STUDY
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:37:41
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

MICE: P16 (INK4A) / (+/-) (C57BL/6) FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
RESPIRATORY SYSTEM						
Lung						
Alveolar/Bronchiolar Adenoma	(14)	(14)	(14)	(15)	(15)	(15)
Alveolar/Bronchiolar Carcinoma	1 (7%)					
Histiocytic Sarcoma	1 (7%)	1 (7%)	1 (7%)			
SPECIAL SENSES SYSTEM						
Harderian Gland Adenoma	(14)					
URINARY SYSTEM						
None						
SYSTEMIC LESIONS						
Multiple Organs	* (15)	* (15)	* (15)	* (15)	* (15)	* (15)
Histiocytic Sarcoma	5 (33%)	1 (7%)	1 (7%)			
Leukemia Erythrocytic					1 (7%)	3 (20%)

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: SPECIAL STUDY
 Route: DOSED FEED

MICE:P16(LNK4A) / (+/-)	(C57BL/6)	FEMALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
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TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	6	2	4	1	1	6
Total Primary Neoplasms	6	2	4			
Total Animals with Benign Neoplasms	1	1	1	1	1	1
Total Benign Neoplasms	1	1	1	1	1	1
Total Animals with Malignant Neoplasms	5	1	3	1	1	5
Total Malignant Neoplasms	5	1	3	1	1	5
Total Animals with Metastatic Neoplasms						
Total Metastatic Neoplasms						
Total Animals with Malignant Neoplasms						
Uncertain Primary Site						
Total Animals with Neoplasms Uncertain-Benign or Malignant						
Total Uncertain Neoplasms						

a Number of animals examined microscopically at site and number of animals with lesion
 b Primary tumors: all tumors except metastatic tumors

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: SPECIAL STUDY
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:37:41
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

	MICE: P16 (INK4A) / (+/-) (C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
DISPOSITION SUMMARY							
Animals Initially in Study	15	15	15	15	15	15	15
Early Deaths	1	1	1	1	1	1	1
Natural Death							
Survivors	14	14	15	14	14	14	15
Terminal Sacrifice							
Animals Examined Microscopically	15	15	15	15	15	15	15
ALIMENTARY SYSTEM							
Liver	(15)	(15) 1 (7%)	(15)	(14)	(15)	(15)	(15)
Histiocytic Sarcoma							
CARDIOVASCULAR SYSTEM							
Heart	(15)	(15) 1 (7%)	(15)	(15)	(15)	(15)	(15)
Histiocytic Sarcoma							
ENDOCRINE SYSTEM							
None							
GENERAL BODY SYSTEM							
None							
GENITAL SYSTEM							
None							

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED)
Study Type: SPECIAL STUDY
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:37:41
TRANSGENIC MODEL EVALUATION II(ASPARTAME) (a)

	MICE: P16 (INK4A) / (+/-) (C57BL/6) MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
HEMATOPOIETIC SYSTEM							
Bone Marrow	(14)	2 (14%)					(15)
Histiocytic Sarcoma	(15)		(15)		(15)		(15)
Lymph Node, Mandibular		1 (7%)					
Histiocytic Sarcoma	(15)	(15)	(15)		(14)		(15)
Lymph Node, Mesenteric			1 (7%)		(14)		(15)
Histiocytic Sarcoma	(15)	(15)	(15)		(14)		(15)
Spleen							
Hemangiosarcoma		1 (7%)					
Histiocytic Sarcoma		1 (7%)					
INTEGUMENTARY SYSTEM							
None							
MUSCULOSKELETAL SYSTEM							
None							
NERVOUS SYSTEM							
None							
RESPIRATORY SYSTEM							
Lung	(15)	(15)	(15)	(15)	(15)	(15)	(15)
Alveolar/Bronchiolar Adenoma		1 (7%)		1 (7%)		1 (7%)	1 (7%)
Histiocytic Sarcoma							
SPECIAL SENSES SYSTEM							
None							

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: SPECIAL STUDY TRANSGENIC MODEL EVALUATION II (ASPARTAME)
Route: DOSED FEED

Report: PEIRPT05
Date: 07/22/02
Time: 08:37:41

MICE: P16 (INK4A) / (+/-)	(C57BL/6)	MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
URINARY SYSTEM								
Kidney		(15)		(15)		(14)		(15)
Histiocytic Sarcoma								
				1 (7%)				
SYSTEMIC LESIONS								
Multiple Organs			*	(15)	*	(15)	*	(15)
Histiocytic Sarcoma			2	(13%)	1	(7%)		

* Number of animals with any tissue examined microscopically

NTP Experiment-Test: 99033-03 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
 Study Type: SPECIAL STUDY
 Route: DOSED FEED

MICE: P16 (INK4A) / (+/-)	(C57BL/6)	MALE	VEHICLE CONTROL	3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM
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TUMOR SUMMARY

Total Animals with Primary Neoplasms (b)	2	2	1	1
Total Primary Neoplasms	2	2	1	1
Total Animals with Benign Neoplasms				
Total Benign Neoplasms			1	1
Total Animals with Malignant Neoplasms			1	1
Total Malignant Neoplasms			1	1
Total Animals with Metastatic Neoplasms				
Total Metastatic Neoplasms				
Total Animals with Malignant Neoplasms				
Uncertain Primary Site				
Total Animals with Neoplasms Uncertain-Benign or Malignant				
Total Uncertain Neoplasms				

a Number of animals examined microscopically at site and number of animals with lesion
 b Primary tumors: all tumors except metastatic tumors

END OF REPORT

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 03
TEST TYPE: SPECIAL STUDY
CONT: N01 ES-65406
PATHOLOGIST: LANNING, LYNDIA

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSCENIC MODEL EVALUATION II (ASPARTAME)

REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:38:13
PAGE: 1
NTP C#: 99033B
CAS: 22839-47-0

REASONS FOR REMOVAL: ALL

REMOVAL DATE RANGE: ALL
TREATMENT GROUPS: INCLUDE ALL

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 03
TEST TYPE: SPECIAL STUDY
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDA
Mice(&strain)

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II (ASPARTAME)

REPORT: PEIRPT08
DATE: 07/22/02
TIME: 08:38:13

NTP C#: 99033B
CAS: 22839-47-0

FOR ALL DOSES THE TUMOR RATES IN THE FOLLOWING TISSUES/ORGANS ARE
BASED ON NUMBER OF TISSUES EXAMINED. IN OTHER TISSUES/ORGANS RATES
ARE BASED ON THE NUMBER OF ANIMALS NECRROPSIED.

Heart
Lung
Pituitary Gland
Spleen

STATISTICAL ANALYSIS OF PRIMARY TUMORS
TRANSGENIC MODEL EVALUATION II(ASPARTAME)

NTP
LAB: BIORELIANCE
EXPERIMENT: 99033 TEST: 03
TEST TYPE: SPECIAL STUDY
CONT: N01-ES-65406
PATHOLOGIST: LANNING, LYNDA

REPORT: PEIRP08
DATE: 07/22/02
TIME: 08:38:13
NTP C#: 99033B
CAS: 22839-47-0

SUMMARY OF STATISTICALLY SIGNIFICANT ($P \leq .05$) RESULTS
IN THE ANALYSIS OF TRANSGENIC MODEL EVALUATION II(ASPARTAME)

Female Mice

Organ

All Organs

Morphology

Histiocytic Sarcoma

Malignant Tumors

Malignant and Benign Tumors

Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Males	12500 PPM	25000 PPM	50000 PPM
All Organs							
Hemangiosarcoma							
TUMOR RATES							
LIFE TABLE							
POLY 3		0/15 (0%)	1/15 (7%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
POLY 1.5		0/14.01	1/14.61	0/15.00	0/14.00	0/14.00	0/15.00
POLY 6		0.0%	6.9%	0.0%	0.0%	0.0%	0.0%
POLY-3 PERCENT (g)							
TERMINAL (d)		0/14 (0%)	1/14 (7%)	0/15 (0%)	0/14 (0%)	0/14 (0%)	0/15 (0%)
FIRST INCIDENCE							
COCH-ARM / FISHERS							
STATISTICAL TESTS							
LIFE TABLE							
POLY 3		P=0.482N	P=0.500	(e)	(e)	(e)	(e)
POLY 1.5		P=0.494N	P=0.508	(e)	(e)	(e)	(e)
POLY 6		P=0.492N	P=0.509	(e)	(e)	(e)	(e)
LOGISTIC REGRESSION		P=0.497N	P=0.505	(e)	(e)	(e)	(e)
COCH-ARM / FISHERS		P=0.488N	P=0.500	(e)	(e)	(e)	(e)
TUMOR RATES							
Dose	VEHICLE CONTROL	3125 PPM	6250 PPM	Females	12500 PPM	25000 PPM	50000 PPM
All Organs							
Hemangiosarcoma							
TUMOR RATES							
LIFE TABLE							
POLY 3		0/15 (0%)	0/15 (0%)	2/15 (13%)	0/15 (0%)	0/15 (0%)	1/15 (7%)
POLY 1.5		0/13.51	0/15.00	2/14.49	0/15.00	0/15.00	1/14.92
POLY 6		0.0%	0.0%	13.8%	0.0%	0.0%	6.7%
POLY-3 PERCENT (g)		0/13 (0%)	0/15 (0%)	1/13 (8%)	0/15 (0%)	0/15 (0%)	1/14 (7%)
TERMINAL (d)							
FIRST INCIDENCE							
COCH-ARM / FISHERS							
STATISTICAL TESTS							
LIFE TABLE							
POLY 3		P=0.487	(e)	P=0.247	(e)	(e)	P=0.515
POLY 1.5		P=0.494	(e)	P=0.247	(e)	(e)	P=0.520
POLY 6		P=0.493	(e)	P=0.247	(e)	(e)	P=0.517
LOGISTIC REGRESSION		P=0.494	(e)	P=0.248	(e)	(e)	P=0.522
COCH-ARM / FISHERS		P=0.329	(e)	P=0.167	(e)	(e)	P=0.515
		P=0.479	(e)	P=0.241	(e)	(e)	P=0.500

		Males			Females		
Dose		3125 PPM	6250 PPM	12500 PPM	25000 PPM	50000 PPM	
All Organs							
Histiocytic Sarcoma							
TUMOR RATES	#	#	#	#	#	#	#
LIFE TABLE							
OVERALL (a)	2/15 (13%)	1/15 (7%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
POLY 3	2/14.01	1/15.00	0/15.00	0/14.00	0/14.00	0/15.00	0/15.00
POLY 1.5	14.3%	6.7%	0.0%	0.0%	0.0%	0.0%	0.0%
POLY 6	2/14 (14%)	0/14 (0%)	0/15 (0%)	0/14 (0%)	0/14 (0%)	0/15 (0%)	0/15 (0%)
POLY-3 RATE (b)							
POLY-3 PERCENT (g)							
TERMINAL (d)							
FIRST INCIDENCE	274 (T)	232	---	---	---	---	---
STATISTICAL TESTS							
LIFE TABLE							
POLY 3	P=0.132N	P=0.492N	P=0.221N	P=0.231N	P=0.216N	P=0.216N	P=0.216N
POLY 1.5	P=0.138N	P=0.476N	P=0.217N	P=0.232N	P=0.217N	P=0.216N	P=0.216N
POLY 6	P=0.138N	P=0.476N	P=0.216N	P=0.231N	P=0.231N	P=0.231N	P=0.231N
POLY-3 REGRESSION	P=0.130N	P=0.517N	(e)	(e)	(e)	(e)	(e)
COCH-ARM / FISHERS	P=0.131N	P=0.500N	P=0.241N	P=0.241N	P=0.241N	P=0.241N	P=0.241N
All Organs							
Histiocytic Sarcoma							
TUMOR RATES	#	#	#	#	#	#	#
LIFE TABLE							
OVERALL (a)	5/15 (33%)	1/15 (7%)	1/15 (7%)	0/15 (0%)	0/15 (0%)	3/15 (20%)	3/15 (20%)
POLY-3 RATE (b)	5/14.00	1/15.00	1/13.55	0/15.00	0/15.00	20.0%	20.0%
POLY-3 PERCENT (g)	35.7%	6.7%	7.4%	0.0%	0.0%	2/14 (14%)	2/14 (14%)
POLY 3	4/13 (31%)	1/15 (7%)	1/13 (8%)	0/15 (0%)	0/15 (0%)	267	267
TERMINAL (d)	219	275 (T)	275 (T)	---	---		
FIRST INCIDENCE							
STATISTICAL TESTS							
LIFE TABLE							
POLY 3	P=0.559N	P=0.062N	P=0.097N	P=0.021N*	P=0.021N*	P=0.306N	P=0.302N
POLY 1.5	P=0.584N	P=0.065N	P=0.085N	P=0.013N*	P=0.013N*	P=0.302N	P=0.302N
POLY 6	P=0.588N	P=0.065N	P=0.079N	P=0.013N*	P=0.013N*	P=0.302N	P=0.302N
POLY-3 REGRESSION	P=0.581N	P=0.065N	P=0.090N	P=0.023N*	P=0.023N*	P=0.321N	P=0.321N
COCH-ARM / FISHERS	P=0.583N	P=0.078N	P=0.082N	P=0.021N*	P=0.021N*	P=0.341N	P=0.341N

		Males		Females	
Dose	VEHICLE CONTROL	3.125 PPM	6.250 PPM	Males PPM	Females PPM
All Organs Malignant Tumors					
TUMOR RATES					
OVERALL (a)	#	#	#	#	#
POLY-3 RATE (b)	2/15 (13%)	2/15 (13%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
POLY-3 PERCENT (g)	2/14.01	2/15.00	0/15.00	0/14.00	0/15.00
TERMINAL (d)	14.3%	13.3%	0.0%	0.0%	0.0%
FIRST INCIDENCE	2/14 (14%)	1/14 (7%)	0/15 (0%)	0/14 (0%)	0/15 (0%)
STATISTICAL TESTS					
LIFE TABLE	P=0.087N	P=0.690N	P=0.221N	P=0.236N	P=0.221N
POLY 3	P=0.087N	P=0.673N	P=0.216N	P=0.231N	P=0.216N
POLY 1.5	P=0.087N	P=0.676N	P=0.217N	P=0.232N	P=0.217N
POLY 6	P=0.087N	P=0.673N	P=0.216N	P=0.231N	P=0.216N
LOGISTIC REGRESSION	P=0.086N	P=0.701	(e)	(e)	(e)
COCH-ARM / FISHERS	P=0.086N	P=0.701N	P=0.241N	P=0.241N	P=0.241N
Dose					
VEHICLE CONTROL	3.125 PPM	6.250 PPM	12.500 PPM	25000 PPM	50000 PPM
All Organs Malignant Tumors					
TUMOR RATES					
OVERALL (a)	#	#	#	#	#
POLY-3 RATE (b)	5/15 (33%)	1/15 (7%)	3/15 (20%)	0/15 (0%)	1/15 (7%)
POLY-3 PERCENT (g)	5/14.00	1/15.00	3/14.49	0/15.00	1/15.00
TERMINAL (d)	35.7%	6.7%	20.7%	0.0%	6.7%
FIRST INCIDENCE	4/13 (31%)	1/15 (7%)	2/13 (15%)	0/15 (0%)	1/15 (7%)
STATISTICAL TESTS	2/19	275 (T)	108	--	275 (T)
LIFE TABLE	P=0.270	P=0.069N	P=0.351N	P=0.021N*	P=0.069N
POLY 3	P=0.235	P=0.065N	P=0.321N	P=0.013N*	P=0.585N
POLY 1.5	P=0.234	P=0.065N	P=0.313N	P=0.013N*	P=0.598N
POLY 6	P=0.236	P=0.065N	P=0.331N	P=0.013N*	P=0.598N
LOGISTIC REGRESSION	P=0.190	P=0.078N	P=0.352N	P=0.023N*	P=0.598N
COCH-ARM / FISHERS	P=0.243	P=0.084N	P=0.341N	P=0.021N*	P=0.623N

Dose	Vehicle Control	3125 PPM	6250 PPM	Males 12500 PPM	25000 PPM	50000 PPM
All Organs Malignant and Benign Tumors						
TUMOR RATES						
LIFE TABLE						
POLY 3		2/15 (13%)	2/15 (13%)	0/15 (0%)	1/15 (7%)	0/15 (0%)
POLY 1.5		2/14.01	2/15.00	0/15.00	1/14.00	0/14.00
POLY-3 RATE (b)						
POLY-3 PERCENT (g)						
TERMINAL (d)		14.3%	13.3%	0.0%	7.1%	0.0%
FIRST INCIDENCE		2/14 (14%)	1/14 (7%)	0/15 (0%)	1/14 (7%)	0/14 (0%)
		274 (T)	232			
STATISTICAL TESTS						
LIFE TABLE						
P=0.340N		P=0.690N		P=0.221N		P=0.236N
P=0.361N		P=0.673N		P=0.216N		P=0.231N
P=0.361N		P=0.676N		P=0.217N		P=0.232N
P=0.361N		P=0.673N		P=0.216N		P=0.231N
P=0.349N		P=0.673N		P=0.500N		P=0.476N
P=0.701		P=0.701		P=0.500N		P=0.475N
P=0.350N		P=0.701N		P=0.241N		P=0.500N
LOGISTIC REGRESSION						
COCH-ARM / FISHERS						
All Organs Malignant and Benign Tumors						
Dose	Vehicle Control	3125 PPM	6250 PPM	Males 12500 PPM	25000 PPM	50000 PPM
TUMOR RATES						
LIFE TABLE						
POLY 3		6/15 (40%)	2/15 (13%)	4/15 (27%)	0/15 (0%)	1/15 (7%)
POLY 1.5		6/14.00	2/15.00	4/14.49	0/15.00	6/15.00
POLY-3 RATE (b)						
POLY-3 PERCENT (g)						
TERMINAL (d)		42.9%	13.3%	27.6%	0.0%	6.7%
FIRST INCIDENCE		5/13 (39%)	2/15 (13%)	0/13 (23%)	0/15 (0%)	1/15 (7%)
		275 (T)	108		275 (T)	267
STATISTICAL TESTS						
LIFE TABLE						
POLY 3		P=0.319	P=0.081N	P=0.360N	P=0.099N**	P=0.033N*
POLY 1.5		P=0.282	P=0.082N	P=0.326N	P=0.033N**	P=0.025N**
POLY 6		P=0.280	P=0.083N	P=0.317N	P=0.040N**	P=0.025N**
LOGISTIC REGRESSION		P=0.283	P=0.082N	P=0.338N	P=0.033N**	P=0.025N**
COCH-ARM / FISHERS		P=0.245	P=0.093N	P=0.093N**	P=0.036N*	P=0.060N
		P=0.289	P=0.107N	P=0.350N	P=0.008N**	P=0.040N*

(a) Number of tumor-bearing animals / number of animals examined at site.

(b) Number of tumor-bearing animals / Poly-3 number

(c)

(d)

(e)

(f)

Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to

pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death.

Logistic regression is an alternative method for analyzing the incidence of non-fatal tumors. The Cochran-Armitage and Fishers exact tests compare directly the overall incidence rates. For all tests a negative trend is indicated by N

(e) Value of Statistic cannot be computed.

(g) Poly-3 adjusted lifetime tumor incidence.

(I) Interim sacrifice

(T) Terminal sacrifice

Tumor rates based on number of animals necropsied.

* To the right of any statistical result, indicates significance at ($P \leq 0.05$).
** To the right of any statistical result, indicates significance at ($P \leq 0.01$).